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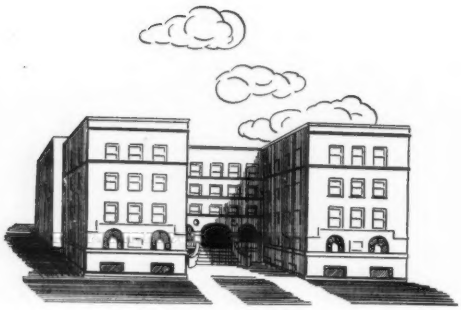

POST-GRADUATE SEMINARS

During the early part of this year, the Educational Committee of the Chicago Medical School Alumni Association mailed a questionnaire to all alumni within a radius of approximately 300 miles from Chicago. The purpose — to seek information regarding the institution of refresher and post-graduate courses for our alumni.

The response was very gratifying, since nearly 350 replies were received. For the past several months the committee, with the aid of special staff members of the school, worked out a varied, interesting, and instructive schedule, in which all features were computed and based upon the wishes of the majority of graduates who responded to the questionnaire.

The program runs through June 29, 1949, and includes a one-hour lecture every Wednesday evening at eight p.m., followed by a half-hour of discussion.

THE DOCTOR AND RELIGION

The Medical Center of Chicago, largest of its kind in the world, is devoting the week of Thanksgiving, 1948, to the development of an understanding of the resources of moral insight and spiritual motivation found in religious faiths so that those who would serve mankind in their professions may equip themselves for the duties and responsibilities which lie ahead. It is the first time that professional schools anywhere have undertaken such a program, and all those who gave freely of their time and energies are to be thanked for their efforts in making this program successful.

Religion, whatever its particular nature be, is a dominant force in our society. It need always be reckoned with if a physician is to understand his patient and prescribe effectively, for organic ailments as well as those of a functional nature.

The physician is also a leader of his community, and to be a true guardian of that coveted position, he must understand the people with whom he lives and works, be they members of his faith or one of the many others. This program, especially if it serves as a model for propagation to other centers of medicine, will do a great deal for the physician-patient relationship, which in recent years has been found sorely lacking in so many instances.

Thirty-five hundred students — in medicine, dentistry, pharmacy, and nursing — form the nucleus for the program which is under the guidance of Dr. Andrew C. Ivy of The University of Illinois, Mr. E. W. Ruehrwein of The Professional Schools' Y.M.C.A., and the faculty of the several schools involved, including Dr. Ryan and Dr. Strong of our Departments of Pharmacology and Anatomy, respectively.

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CARCINOMA AS A GYNECOLOGICAL PROBLEM

By DR. E. FISCHMANN, M.D.

Professor and Chairman of the Department of Obstetrics and Gynecology

WOMANKIND today, more than ever before, is cancer-conscious, and rightly so, as it is estimated that there are at present nearly 500,000 sufferers from this disease and that fully one-half of this number is in women, the primary lesion being in the breast or the pelvic organs. About 30,000 women die annually from cancer of the uterus.

It is well known that for years tuberculosis headed the list and carcinoma was in second place of all mortality tabulations, but tuberculosis has been pushed down to anywhere between sixth and tenth place in the last two decades while carcinoma retains its prominent place and role as a destroyer of human life, especially the middle-aged female.

Tuberculosis was and still is an incurable disease in its advanced stages, but amenable to treatment in the early phases. Through a campaign of education, enforcement of sanitation, isolation of active cases, periodic examinations of sputum, more or less routine X-ray chest examinations of all school children, college students, factory workers, food handlers, nurses, etc., cases of tuberculosis have been discovered in their incipiency and treated, and countless numbers of lives have been saved. Such in brief is the history of the conquest of the White Plague.

Has the medical profession and the gynecologist been dormant and unmoved by the frightful suffering of women afflicted with pelvic carcinoma and the appalling number of lives lost on account of this disease? Let us now analyze and review categorically what has been done to help stamp out or lessen the ravages of pelvic cancer.

Cancer, like tuberculosis, is incurable in the advanced stages of the disease, no matter where it originates.

Any of the female sexual organs may be the primary seat of this disease, but the uterus is by far the most commonly affected organ, and therefore we will confine our remarks to carcinoma of the uterus.

In the uterus, carcinoma starts either from the mucosa of the body or from the mucosa of the cervix. Whether it springs from the corporal mucosa or endometrium, or from the cervical canal mucosa, the endocervix or the mucosa on the vaginal aspect of the cervix, the portio, it may exhibit either a papillary pattern or an ulcerated lesion or both. In either event, the growth is friable, which means that portions of the growth may break off and cause varying degrees of bleeding. Friability of cervical neoplasm was considered a very important diagnostic sign and in the past, lesions were allowed to grow and were watched by the doctor until friability could be demonstrated, but nowadays this watchfulness is considered bad practice.

Up to about three decades ago, all standard textbooks listed the cardinal symptoms of Uterine Cancer as hemorrhage, foul-smelling leucorrhea, pain, secondary anemia and loss of weight, and the majority of sufferers did not present themselves until they had pain or most of these enumerated symptoms, which were manifestations of the advanced stages of the disease and not amenable to treatment, and hence, the high mortality. Pain in uterine carcinoma is a late symptom and signifies the extension of the disease beyond the confines of the womb, and the same is true of loss of weight and secondary anemia.

Then, through a concerted effort by several gynecologic and philanthropic bodies, a movement of education was set afoot, urging all women to have periodic examinations by their physicians at least twice a year. Then a plea was made to all women past the menopause who exhibited any evidence of blood, whether after exertion, coitus or a long automobile ride, to present themselves for examination to rule out the possibility of carcinoma.

As time went on there was a modest response from the rank and file, but never a generous one. Women, some apparently in good health and others with spotting after the menopause, presented themselves, were examined bimanually, and, if a lesion of the cervix was present, a biopsy was done, or if the bleeding came out of

the cervical canal, a diagnostic curettage was performed.

Biopsy of the cervix, the removal of a piece of diseased tissue from the cervix, and diagnostic curettage, the removal of endometrium for careful examination by an experienced pathologist, spelled a very definite advance in the diagnosis and treatment of uterine cancer. Some objection was raised from time to time against the indiscriminate cutting into a malignant lesion and the danger of spreading the lesion, but by now all fears of this happening have been expelled.

Hinselman, of Altona, devised a colposcope, hoping by its magnification and intense illumination to be able to pick out areas suitable for biopsy. Then Walter Schiller, of Vienna and later of Chicago, hoped to be able to detect early carcinoma of the cervix by bathing the cervical mucosa in an iodine solution. Normally, the vaginal aspect of the cervix becomes mahogany brown when this tintorial test is carried out, because healthy vaginal epithelium contains glycogen. Diseased epithelial cells, carcinoma cells especially, do not contain glycogen and hence fail to take the dark stain, and thus the suspected area stands out and can be biopsied for microscopic study. Unfortunately, neither of these tests withstood the test of time.

Then, too, it must be remembered that carcinoma of the body and cervix of the uterus, only too frequently occurs in women who are still menstruating and these individuals usually exhibit some intermenstrual bleeding. These, too, are in need of careful bimanual and specular examination and frequently of a cervical biopsy or diagnostic curettage. Cervical carcinoma especially, may occur at the end of the second or any time during the third decade of life; it is not necessarily a disease of middle life and advanced years.

As a result of intensive studies of the changes occurring in the epithelium of the female genital tract, Papanicolaou and Trout, in 1943, introduced the so-called Vaginal-Smear Method of Cancer Diagnosis. This test is based upon the knowledge of friability of genital carcinoma, the breaking off of pieces or shedding of individual malignant cells, and these are deposited in the posterior fornix or vault of the vagina, and when proper smears are made and stained according to the method developed by Papanicolaou, cancer cells can be demonstrated.

This test, which is a distinct innovation in diagnosis of pelvic carcinoma, is on trial in several large medical centers, but it is too early to predict the future of it and if it will gain a permanent place in cancer diagnosis. Many valuable and instructive papers are appearing in the literature weighing the pros and cons.

In several laboratories in the East it has been used as a routine test in gynecologic cases and positive smears have been obtained in cases where no cancer was suspected, and in several of these cases the positive diagnosis was confirmed by diagnostic curettage, cervical biopsy, or after a hysterectomy.

This test is also being used in the routine examination of women who have no pelvic complaints, and in 1 to 4% of the women so examined, positive smears have been obtained before the woman had any spotting or bleeding. Thus, it may be used as a screening method and it is so employed in several Cancer Detection Clinics.

It requires special cytological training to carry out this procedure, but the enthusiasts contend that the diagnosis is not difficult as the cancer cells appear rather large, have a small amount of cytoplasm, and a large, deep staining nucleus with large granules. Pathologists who are accustomed to study cell pattern, invasion, mitosis, and variations in size and staining of cells in tissues, are not ready to accept this method or predict a brilliant future for it.

The present status of this method may be summarized:

1) The vaginal smear method should be given a thorough and impartial trial for its proper evaluation.

2) While it probably never will become a routine office procedure, doctors should know how to take the smear. According to Papanicolaou and his co-workers, it is taken from the vault of the vagina, but others recommend a direct smear from the cervix. As soon as the smear is made it should be placed in a mixture of equal parts of 95% alcohol and ether. Then it should be stained or sent to a laboratory established for this special purpose as the Montreal group has done.

3) All positive smears should be checked by biopsy or diagnostic curettage, thus to play an adjunct role.

4) Some predict that this method will help to stimulate pathologists to a greater interest in cell structure and cell changes in tissues.

5) This test has proved of value and has great potentialities in checking cases post-operatively or post-radio-therapeutically.

Before the introduction of radium and x-ray into gynecology, most of the cases of uterine carcinoma that were deemed operable were subjected to the radical Wertheim Hysterectomy, which carried with it a high immediate mortality and a five-year survival rate of 18% to 25%.

Since 1921, when radium was used more or less to the exclusion of radical operation, the immediate mortality fell, and the five-year survival rate rose to 20 to 25%.

Nowadays, most gynecologists are resorting to the radical hysterectomy with pre-operative and post-operative irradiation, and we are proud to say that the statistics are a little more encouraging, thanks to better anesthetics, blood transfusions and antibiotics, which have helped to lessen the immediate operative mortality and to get five-year cures in 31% of the cases.

Let us hope that the Papanicolaou smear method may further help in the early diagnosis of pelvic cancer; that when used as a screening method it will detect early symptomless pelvic carcinomata, and that it will prove valuable in detecting the results of radio-therapy and the detection of early recurrences.

In conclusion, it must be said that the earlier the carcinoma is detected and the earlier treatment is instituted, the better will be the results.

ELECTROPHORESIS IN BIOLOGY AND MEDICINE

By DR. A. ROBERT GOLDFARB, M.S., Ph.D.

Department of Biochemistry of The Chicago Medical School

ELECTROPHORESIS is the motion of a charged particle, suspended or in solution, under the influence of an electric field. This motion is shown by a large variety of particles which have dimensions of the order of 0.5 to 1.0 mu. In Figure 1 is shown a diagrammatic representation of a number of suspended particles indicating the direction and magnitude of the velocity of motion.

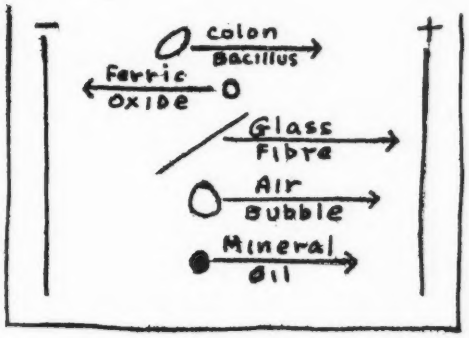

Figure 1

In the case of the inert particles such as air, etc. the charge is due to an interfacial potential that always appears at any interface. In the other cases the charge is attributed to the presence of charged groups in the molecules making up the particles. If the *pH* of the solution is varied the inert particles do not change their mobility, whereas the other particles change the velocity and may change the direction of motion. If there is added to the suspension a neutral solution of gelatin all the particles move in the same direction and with very nearly equal velocities. This motion is independent of the shape or size of the suspended particle. This uniformity of response in the gelatin solution leads to the obvious conclusion that, 1) all the particles have the same surface and surface charge when placed in the gelatin solution, and 2) the mobility is dependent principally on the surface charge and is not related to the density, chemical composition (excepting insofar as it affects the surface), shape, size or molecular weight of the particle as a whole.

The original observations on the motion of suspended particles was made about 100 years ago, but the theory of this behaviour and its extension to other systems was not elucidated until early in this century by Pauli, Abramson, Loeb, Freundlich, and others. The apparatus, used for the observation of this phenomenon, consists of

a narrow cell mounted on a microscope stage and fitted with appropriate equipment for imposing an electric field in the cell. The measurement of the direction and velocity of motion is done by direct visual examination.

The work was extended to include dissolved macromols. The progress was fairly slow until Tiselius published a report on a new type of apparatus which utilized the Toepler method for determining refractive index changes and which eliminated other serious experimental faults. The equipment described enabled the determination not only of the number of dissolved macromols but also a good estimation of the relative amounts of each constituent. Improved procedures were rapidly developed by Lamm[16], Philpot[17], Svensson[18], and Longsworth[9]. A schematic diagram of the Longsworth modification of the Tiselius equipment is given in Figure 2.

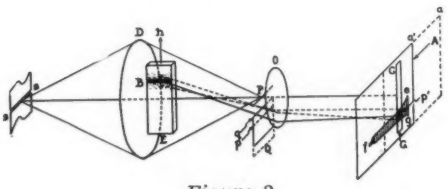

Figure 2.

The light source S-S is focused by the schlieren lens D at the point P which is in the same plane as the schlieren diaphragm Q. The camera lens O is focused on the cell E and forms an image of the cell on the screen at G-G. If the fluid in the cell is homogenous the image G-G appears uniformly illuminated. If there is a boundry B in the cell between the protein and buffer solutions, a concentration gradient of protein exists, and therefore also a refractive index gradient which varies with the height in the cell. The light which passes through the boundary is deflected downward and is brought to a focus in the same plane as Q but lower than the normal focus at P. If now the opaque diaphragm Q is raised, it will first block out the deflected ray at P and a dark band appears on the screen which is conjugate to the region of highest concentration in the boundary B. This point is shown as P′ on the screen. The boundary, however, is not a single plane but a region having a finite thickness and in which a concentration gradient exists along the height of the cell. The concentration gradient is Gaussian in form, i.e., the edges have the lowest concentrations and at some intermediate plane the concentration is maximum. Since the refractive index changes with the concentration, a similar curve is obtained for a plot of refractive index vs. height in the cell, and various layers within the boundary are deflected downward to varying extents but always below the image of the incident beam. As the schlieren blade is raised further, more of the deflected beam is blocked and a larger band appears on the screen. In the Longsworth technique, as the schlieren blade is raised, a photographic plate, at the screen position, is simultaneously moved by a system of gears in the direction A. This forms a pattern on the plate as shown in the figure. The plate will show a light pattern on a dark background which when reproduced gives the pattern as black against a light background. For ease of observation, the diagrams are turned through an angle of 90°.

As can be inferred from the experiments with suspended particles, the electrokinetic properties of a charged dissolved molecule depend on the surface charge and detailed mathematical and physical analysis has shown that the major factor is the charge density on the surface of the molecule. The molecular weight has very little or no influence on the mobility and, in fact, many cases have been found of dissolved proteins which were shown to be electrophoretically homogenous, but which on analysis in the ultracentrifuge have been shown to be a mixture of similary charged proteins of varying molecular weights. The direction of motion of a dissolved protein is a function only of the *pH* of the medium and is stationary at the isoelectric point. The actual velocity is a function not only of the *pH* but also of other properties of the medium, which may be grouped as "retarding forces," e.g., ionic strength, size and charge on the ions of the medium, viscosity, etc.

Normal Serum and Plasma

In 1937, Tiselius[1] studied the electrophoretic behaviour of normal serum. Instead of obtaining a pattern consistent with the chemical findings of that time, he obtained a pattern consisting of four peaks with definite mobility and one stationary peak. The four peaks he termed, in descending order of velocity: albumen, alpha, beta and gamma globulins. The stationary peak on the ascending side, i.e., boundary moving into

buffer solution, he termed the delta boundary; and on the descending side, i.e., boundary moving into the protein solution, he termed the epsilon boundary. In Figure 3 is a tracing of a normal serum pattern as obtained later with more efficient media (see below).

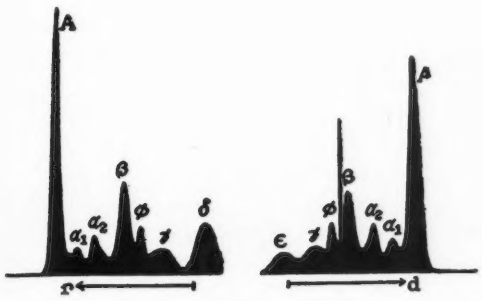

Figure 3.

Studies of the delta and epsilon boundaries by Longsworth[9], et. al., showed them to be due to a change of buffer concentration at those points and not to any protein constituent. When plasma was studied the peak for fibrinogen appeared between the beta and gamma peaks. To correlate this pattern with chemical findings, Tiselius and Svensson[3] showed that pseudoglobulin contained 85% alpha and 15% gamma globulins and the euglobulin contained more beta and gamma and less alpha globulins. These patterns were rapidly confirmed by a variety of investigators and the Tiselius terminology is now in general use for the description of blood proteins.

In making an electrophoretic analysis of a mixture of proteins the chemical composition of the buffer salts is of great importance and in many cases a change of buffer salt is necessary to obtain the maximum separation. For example, in human plasma and serum the best separation is obtained with a veronal buffer at pH 8.5 and a concentration about 0.1 Molar, in which case the pattern is that shown in Figure 3. In phosphate buffer at pH 7.7 and with Lithium Veronal buffer at pH 7.9, the alpha-1 boundary fails to separate from the albumen and the gamma peak tends to fuse with the delta and epsilon boundaries.

Examination of the patterns in Figure 3 shows on the descending side and adjacent to the beta peak, a very thin spike which is known as the beta anomaly. The spike was early shown to be due to a slight opacity in this plane. Dole[4] showed that the anomaly disappears when serum stands 10 months, or can be abolished by extraction with fat solvent of the serum. It was early suspected that the beta globulin contains a large amount of lipids and this was rapidly confirmed. All the fractions of the blood have been separated and shown to be conjugated, thus albumen contains carbohydrates, lipids and bilirubin, alpha and beta globulin contain lipids and most of the antibodies, as will be shown move with the gamma globulin.

Albumen-Globulin Ratio

The patterns that are obtained can be used not only to show the presence or absence of a constituent protein but also obtain the quantitative proportions of each constituent present in the solution. If it is assumed that the refractive index-concentration ratio of all the proteins is the same, and this was recently demonstrated by Longsworth[9], it can be shown that the area under each peak is a measure of the concentration of that constituent. It will be found that, if the total area of the curve is measured at various times during an electrophoretic run, this area will remain constant in spite of the marked change of shape of the curve. Of course, from the ratios obtained in this manner and the chemical determination of the total protein, it is possible to determine the absolute concentration of each constituent.

By utilizing this method a value of the A/G ratio can be obtained and compared with those values obtained by chemical means. It was found early in the studies by the electrophoresis technique that values by this means were lower than those obtained by salting-out methods. Investigation by several groups showed that the albumen obtained by salting-out methods contained considerable globulins. Even the early electrophoresis values were too high because the alpha-1 component moved with the albumen when the early inadequate buffers were used (*vide supra*).

Dole and Braun[5], using the sodium veronal buffers of 0.1 molarity and at pH of 8.5, obtained the clear separation shown in Figure 3 and found values of 1.5 to 1.8 for normal blood. The values of Braun and Dole for 15 normal adult males are given in Table 1.

		Albumin		α_1		α_2		β		ϕ		γ		A/G
		gm.	gm. per 100 cc.	gm.	gm. per 100 cc.	gm.	gm. per 100 cc.	gm.	gm. per 100 cc.	gm.	gm. per 100 cc.	gm.	gm. per 100 cc.	
Concentration	Mean	0.603	4.94	0.046	0.31	0.072	0.48	0.121	0.81	0.051	0.36	0.110	0.76	1.53
	Standard deviation	0.028	0.27	0.007	0.051	0.013	0.083	0.019	0.126	0.006	0.059	0.025	0.151	0.181
Mobilities (cm^2/volt sec. × 10^5)	Mean	5.06		5.07		4.08		2.83		2.14		1.82		
	Standard deviation	0.267		0.256		0.256		0.241		0.252		0.282		

Table 1.

To date, no difference of pattern, mobility or ratios have been found in normal human bloods for reasons of age or sex. Longsworth, Curtis and Pembroke[6] compared the maternal and fetal plasma of ten women. The maternal plasma showed a greater deviation from normal than the fetal plasmas. The maternal plasma has a greatly increased beta peak which can be correlated with the lipid carrying property of beta globulin, and the fetal plasmas showed a high gamma peak corresponding to the known high immunity of the new born.

In view of the variety of buffers used until recently, it is not possible to make a statistically significant statement of the range of ratios of the various blood proteins for normal humans, and, at this time, only gross changes of pattern are considered significant.

Before examining the patterns obtained in various types of pathology, it would be of interest to indicate what is the effect of various treatments to which blood may be exposed[7]. Long standing at —20°C. has no effect on pooled blood. Lyophophilisation of plasma causes no change of pattern. Drying of serum or plasma at room temperature causes a decrease of A/G ratio. Unrefrigerated and autopsy specimens show marked changes.

Pathological Sera, Plasma and Body Fluids

It would seem logical to assume that the state of health of the body as a whole, or of any tissues,, would be mirrored in the blood, and indeed studies of sera, plasma and body fluids in disease showed marked changes. In one of the earliest studies, Hesselvik[8] reported that in pneumonia alpha globulin increased while all other constituents were relatively unchanged. Longsworth, et. al.[9] confirmed this and extended this finding to febrile bloods resulting from rheumatic fever, pneumonia, and peritonitis. In these cases the alpha globulin albumen ratio increased from a normal value of 0.15 to the pathological value of 0.30.

In a broad study of a large variety of pathological conditions Longsworth, Shedlovsky, and MacInnes[9] demonstrated the marked variation in patterns in disease. Some of the results are shown in Figure 4.

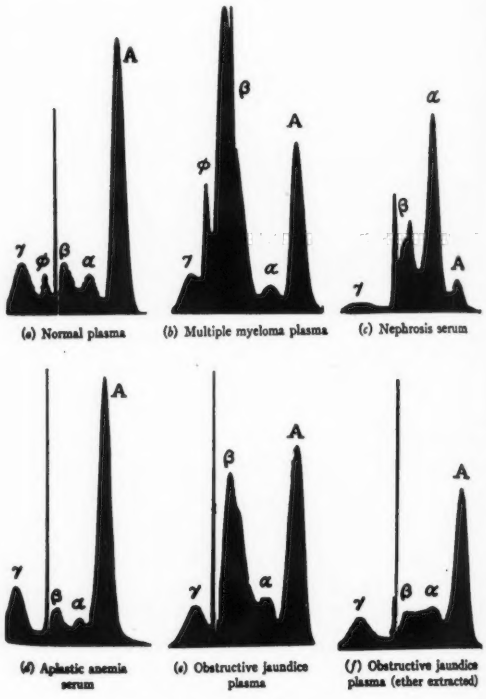

Figure 4.

Infectious Disease

Leutscher[10] studied several plasmas and effusions in Lobar pneumonia. The plasma albumen decreases, alpha globulin almost doubles, and beta and gamma globulin and fibrinogen increase to a variable extent. Analysis of the exudates gave no evidence of the selective secretion of any one protein constituent.

Dole and co-workers[4] studied 6 cases of scarlet fever, three of which developed rheumatic fever. Significant changes occurred for both types of cases. In the early stages of the disease albumen and alpha 1 and 2 globulins decrease sharply. The gamma globulin increases regularly with the progress of the disease and a definite correlation could be drawn between the titer of anti-streptolysin and the increase in gamma. No detectable amount of gamma globulin could be removed by absorption on the live streptococcus

of the strain responsible for the infection. In the rheumatic fever cases the same picture was obtained, but more slowly.

The principle studies of tuberculosis were made by Leutscher [10] and Seibert[11]. In plasma the albumen decreases to a variable extent, whereas alpha and gamma globulin and fibrinogen increase, the gamma in active cases. In the pleural effusions and ascitic fluid the protein is high, with a component distribution similar to the plasma. Tuberculin preparations were separated electrophoretically into several fractions containing proteins conjugated with polysaccharides and nucleic acids. Two purified proteins of different molecular weights were isolated which, when injected into rabbits, elicited an antibody response and traveled with the alpha and gamma globulins.

Immunization and Hyperimmunization

A great many studies have been made on the change of pattern of sera of experimental animals during immunization and hyperimmunization with bacterial antigens and foreign proteins. Tiselius[3] and Kabat[2] showed, for example, that the antibody of highly potent egg albumen of rabbits migrated with the gamma globulin. The same workers were also able to show that anti-pneumococcus type I horse serum gave a component moving with a mobility intermediate between the beta and gamma globulins. The corresponding antibodies in rabbit, pig and monkey formed a part of the gamma globulin. The effect of continuing hyperimmunization on horse serum is illustrated in Figures 5 and 6. In all cases it should be noted that the gamma globulin shows a very high peak.

Bull[19], et. al. found in fresh sera of 13 patients suffering from syphilis in the primary, secondary and tertiary stages that the beta anomaly was absent. It is reported that in several cases where false positives were obtained with the Wasserman and Kahn tests the beta anomaly was present.

Non-Infectious Diseases

In obstructive jaundice it has been reported[9] that a large amount of material is present that migrates with beta globulin and which disappears on extraction with ether. Gray and Barron[12], however, show in a case of extrahepatic jaundice caused by gallstones there is no change in the electropheretic pattern.

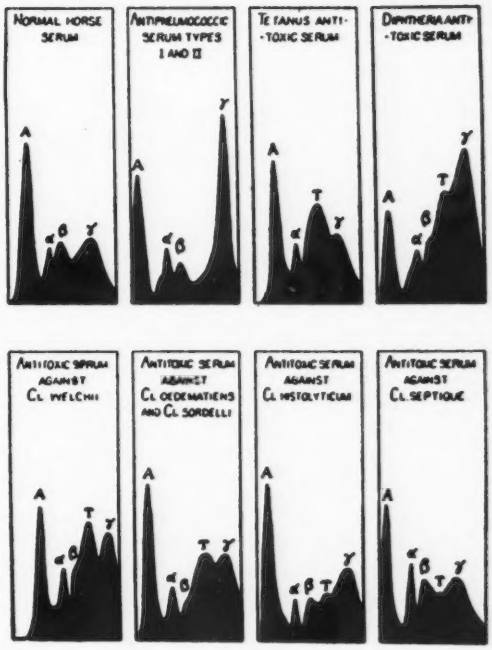
NORMAL HORSE SERUM
ANTIPNEUMOCOCCIC SERUM TYPES I AND II
TETANUS ANTI-TOXIC SERUM
DIPHTHERIA ANTI-TOXIC SERUM
ANTITOXIC SERUM AGAINST CL WELCHII
ANTITOXIC SERUM AGAINST CL OEDEMATIENS AND CL SORDELLI
ANTITOXIC SERUM AGAINST CL HISTOLYTICUM
ANTITOXIC SERUM AGAINST CL SEPTIQUE

Figure 5.

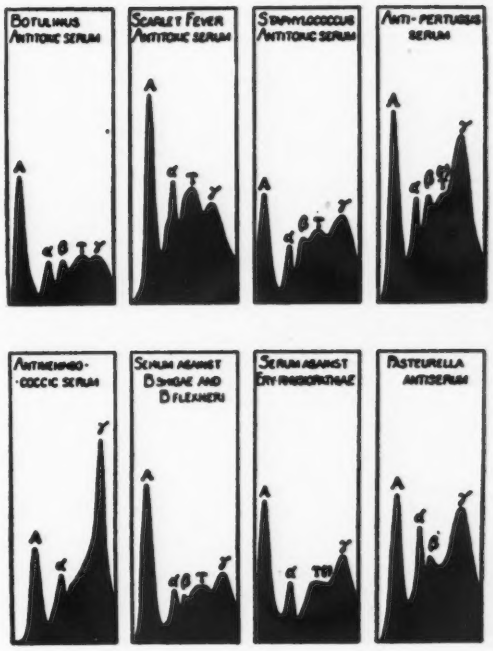

Figure 6.

In cardiac failure plasma albumen decreases and beta and gamma globulin increase, and alpha globulin and fibrinogen suffer no change[10].

In most renal disorders it has long been recognized that the A/G ratio decreases. The earliest electrophoretic studies of nephrotic sera and plasma were made by Longsworth, Shedlovsky and MacInnes[9]. As would be expected, the patterns are markedly altered. The albumen shows a marked reduction while the alpha-2 and beta globulins are increased. The urines of these patients show a pattern similar to that of normal serum. This is in direct contradiction with the previously held concept that all the urinary protein is albumen. Bourdillon made an electrophoretic and osmotic study of the serum and urinary albumens in nephrosis and was able to show that they had different properties. Leutscher[10] studied 5 cases of glomerulonephritis and indicated that albumen and beta globulin were only slightly altered. The corresponding urines showed normal serum patterns.

In hyperthyroidism low absolute and relative concentrations of albumen are obtained, accompanied by an increase of alpha globulin and fibrinogen. Several months after thyroidectomy the blood patterns returned to normal[13]. Hypothyroids, caused by either thyroidectomy or x-ray treatment, showed a low albumen and greatly increased beta globulin. Therapy returned the blood patterns to normal.

Injection of gonadotrophic extract from human pituitary into goats gave an increase in gamma globulin corresponding to an increase in anti-hormone activity[14]. Electrophoretic separation showed all the anti-hormone activity to be in the gamma globulin fraction.

In severe cases of diabetes mellitus the albumen decreased, the beta globulin increased greatly and the total protein is normal. In mild cases the total protein is slightly lowered but the pattern is normal. Successful therapy results in a normal total protein and pattern.

In Addison's disease the total protein is in the high normal range, the albumen decreases and the globulins increase[10]. Desoxycorticosterone therapy has no influence on the blood patterns, whereas crude adrenal extract restored the pattern to normal. It is interesting in this case to note the utility of the electrophoretic technique to determine how complete recovery has been obtained with a given treatment.

Stern and Reiner have reported two cases of hypoproteinemia, a 12-year-old girl whose case was followed from birth, and a 3-year-old boy. All attempts to raise the protein level were only partly and temporarily effective. In both cases the beta globulin peak is absent or vanishingly small. In spite of the absence of this "antibody carrying" constituent, it is reported that the 12-year-old girl has been found remarkably free from infection.

In the study of cancer some work has gotten under way. Alling is stated to have reported that of 125 cancer patients only one showed a normal pattern. The details of this work have not appeared as yet. More recently Peterman, Karnofsky, and Hogness found that in gastric ulcer, the hypoproteinemia is entirely due to the decrease in albumen, all other proteins are normal. In gastric cancer the albumen is reduced somewhat and alpha globulin and fibrinogen increase. After removal of the tumor the fibrinogen and alpha globulin return to normal in a few weeks, whereas the increase of albumen is extremely slow even in patients in a strongly positive nitrogen balance. The same group reports that if the electrophoresis is carried out at a pH of 4.0, a new "acid protein factor" is shown to be present which in normals has a concentration of less than 100mg%. In cases of gastric cancer, cancer of the lung, lymphatic leukemia, and Hodgkin's disease, the concentration is greater than 100 mg.%. In six cases of patients surviving gastrectomy for cancer for more than one year, the values of the factor returned to normal.

* * * * * *

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(Continued on page 29)

FROM AN ADDRESS DELIVERED AT THE SENIOR PROM AT THE SHERRY HOTEL, CHICAGO, JUNE, 1948

DR. MAURICE OPPENHEIM, M.D.

Professor of Dermatology, The Chicago Medical School

YOU Seniors have finished your formal studies and in the near future you will have your graduation. I do hope that after one year internship you will be licensed; then you will be on your own feet, on your own responsibility. Nobody will be in control of you, only your own conscience.

When the students graduated at the University of Vienna, there was a solemn ceremony and celebration. From all countries of Europe, sometimes from the entire world, came relatives of the students who were graduated.

The Rector of the University was seated in front of the hall upon a throne, below him the Dean of the Medical Faculty, the Pro-Rector and the Pro-Dean, both of the past year, all dressed in velvet gowns trimmed in ermine, with golden chains over their breasts, which carried the golden seals of the University and of the Faculty. One of the Professors of the Medical Faculty was the Promotor; who took the oath from the students. They were dressed in white tie and tails. Most of the suits did not fit very well, especially the trousers, which were too long or too short. They were previously worn by many doctors, now prominent in public life. The students had to place their fingers on the Sceptre of the University while the Promotor read the oath which was similar to the oath of Hippocrates, in Latin, and handed the diploma to the Doctor. The diploma was in Latin, and was written on parchment with the seal of the University. He became a Universae Medicinae Doctor (M.U.Dr.) and already had the license to practice. No state board examinatinon was necessary.

The University of Vienna with the four Faculties, Theology, Jurisprudence, Medicine, and Philosophy, formed a state within a state. It was independent; had its own laws and rules, which we understand if we follow the historic development of the Universities in Europe. At times the Rector has more power than the Mayor of the city. Some of these laws are still in effect; police are not allowed to enter the so-called academic ground of the University. If there was a fight between the different groups of students, which happened very often in the last years, the Rector and the Deans and their staff had to restore order, and usually they succeeded.

Let us return to modern times; I would like to give you a picture, as brief as possible, of the method of studying medicine in Vienna; and to illustrate this I would like to tell you how I myself graduated as a Universae Medicinae Doctor of the University of Vienna. After four years of grammar school, I entered the Akademic Gymnasium in Vienna, founded 600 years ago, where I studied eight years. The Gynasium is nearly the same as your high school and college. The most important studies in the Gymnasium were: Latin eight years, and Greek six years, as a preparation for the medical studies. How often I regret that my students here do not understand Latin and Greek. The names of diseases are Latin and Greek, originating from the old Greek and Roman writers like Hippocrates, Galenus, Celsus, etc.; occasionally Latin, like *Lupus Vulgaris*, that means "common wolf" (not as you understand "wolf") because the skin is eaten up gradually and slowly; occasionally Greek, like *Diptheria*, from the Greek word "diapthero," to destroy; occasionally both languages together, like *Psoriasis Vulgaris*, "psora," the scale, and "vulgaris," common.

At the end of the Gymnasea study, there was an examination, the "Matura," that meant you were ready to visit a University. It was a very severe examination, especially in Greek and Latin, and many pupils failed. My medical studies at the University embraces six years, interrupted by half a year of military service in the infantry, which I left with the high rank of Corporal. The service in the infantry is to teach the Doctor what a soldier in the infantry is able to stand. We had to march as much as ten hours with heavy tornisters and guns. In the Viennese University there were no quarters, only semesters; the winter semester from October to Easter and the summer semester from Easter to July. At the end of July came vacation to the first of

October, nearly two months. I had to write the so-called pre-examinations, Minerology, Botany and Zoology, which are now replaced by one examination of Biology. The first Rigorosum (rigorous severe examination) took place after five semesters; the second and third, after ten semesters.

The first Rigorosum consisted of Anatomy, Histology, Embryology, Physiology, Chemistry, and Physics. The second Rigorosum, Pathology, Internal Medicine, Pharmacology; and the third Rigorosum, Surgery, Ophthalmology, Obstetrics and Gynecology, Legal Medicine, Dermatology, Pediatrics, Psychiatry and Otiatry: the three latter not being compulsory.

My most prominent teachers were Zucker and Kandl in Anatomy, the successor of Hyrtl; Albert and Gussenbauer in Surgery, Weichselbaum in Pathology, Nothnagel in Internal Medicine; Wertheim in Obstetrics and Gynecology; Fuchs in Ophthalmology; Kraft Ebing and Wagner-Jauregg in Psychiatry; Esner in Physiology; Ebner in Histology; and Pollitzer in Otiatrics.

The Rigorosums were only oral, and divided into two parts, the practical part was called "Practicum," and the theoretical part called "Theoreticum." The student had the choice of the Professor in those fields, where two or more Professors were available. A group of 4 to 6 students were examined simultaneously, a representative of the Government and of the Faculty, usually the Dean, were present. The examinations were held publicly and many students attended the examinations, where they learned very much, and prepared themselves for their examinations. The grades were only three: Excellent, Sufficient and Not Sufficient; there was no percentual evaluation. I remember one of my friends whom I assisted at the Practicum of Surgery, and who failed, asking Professor Gussenbauer, the examiner, what book he should study. The answer was: Study the "Hand-book of Surgery," Winiwarter-Billroth, about 30 volumes. A re-examination time depended upon the examiner, 3 or 6 or 12 months. Repeated failures were followed by exclusion from the Medical Faculty.

What are the main differences between the ways of studying medicine at the Viennese University and The Chicago Medical School?

1. No roll call. From the moment the student enters the University he is a free man. It is completely up to him to study, to attend lectures and practical exercises; only in obstetrics did he have to prove his regular presence in an obstetrical clinic. A University clinic in Vienna is totally different from what you understand here. Here, it is an out-patient dispensary; in Vienna it is a unit of hospital beds, lectures of the Professors and his assistants, research, out-patients' treatments, all united, and under direction of the Professor of the University Clinic. The student has only to prove by the signature of the Professor that he has made the inscriptions of the compulsory subjects.

2. No written examinations; every examination, practical or theoretical, is oral; you have to face the Professor for 15 or 20 minutes, sometimes longer. According to my experience over nine years at The Chicago Medical School, the written examinations have the disadvantage that the Professor has no idea how the student is thinking. There is mostly memory work. Those who have the better memory, get better grades. Very few students are interested in the mistakes they made; if they are passing, even with a "C" grade, they do not ask me why they got a "C," only if they fail do they ask, and occasionally not even then.

3. The Professor, head of the department, instructs the students. The lectures are free, no book, no script. Post-graduate courses and instructions are held by the assistants.

4. There are no animal experiments by students. The Professors perform and present them in Vienna.

5. There is no internship and no state board examinations. Usually, the promoted Doctors have four years of rotating service in one of the Government hospitals before going into practice. This is not compulsory. There are others, but only minor differences. These mentioned have their advantages and their disadvantages. These rules were developed during the existence of the universities through many centuries; the University of Vienna was founded in the middle of the 14th century. I believe that by a combination of both methods, of teaching and examining, the student would learn more and in a better way. The study of Medicine is now centered in the U.S.A., and especially here in Chicago. History is now repeating itself. From the Greek and Roman schools (Hippocrates, Galenus) the med-

ical schools shifted to the Jewish and Arabian schools (Maimonides and Avicenna); from them to the Italian and Spanish schools (Morgagni); later to France (Ambroise Pare and Pasteur); to England (Harvey), and finally to the German and Austrian schools (Koch, Billroth, Hebra, Rokitansky, and Freud).

The future will show that the greatest progress in Medicine will be made from now on here in the U.S.A., since the recovery of Europe will take a long time. I do not believe that the main School of Medicine will ever be established on the Continent again; and I believe that our school, The Chicago Medical School, will play a big role in this regard under the leadership of our honored Dean, John J. Sheinin, who was able to move our school—despised by others, but loved by us—to the rank of other medical schools and to keep it open to all medical students of every creed, race and color. And therefore, you Seniors and I, have to join in expressing our deepest thanks to this man, who devoted all his strength and all his time to The Chicago Medical School.

THE PATHOLOGY OF CARCINOMA OF THE STOMACH

By DR. B. H. NEIMAN, M.D.

Department of Pathology of The Chicago Medical School

THIS discussion will be based upon the material coming to autopsy at the Cook County Hospital. Every hospital has clinical material which is more or less peculiar to that institution. What I shall tell you is, therefore, somewhat different from the usual discussions found in textbooks.

Carcinoma of the stomach was formerly considered to be the most common type of carcinoma in males. According to various statistical data, between 35 and 45 per cent of all carcinomas are located in the stomach. A few years ago we found carcinoma of the stomach comprising about 25 per cent of all malignant tumors which came to autopsy. During the past ten years, carcinoma of the lung seems to be more common than carcinoma of the stomach, at least according to our experience.

The disease is more common in the male than in the female. The average age incidence is between 50 and 70 years. The youngest patient in our series was a man of 18 years. There are cases reported in the literature of carcinoma of the stomach in children. One case of congenital carcinoma of the stomach has been reported.

There are two main theories concerning the etiology of carcinoma of the stomach: one stressing embryological malformations or disturbances in development; the other one emphasizing acquired pathological conditions.

The congenital theory is supported by the following facts:

That there is an hereditary predisposition to carcinoma of the stomach, there can be no doubt. But what is there in the histology of the stomach that we can correlate with this theory? Examination of the normal stomach histologically shows, from time to time, islands of intestinal glands in the mucosa. These islands are usually found in the lesser curvature and in the region of the pylorus, i.e., in those locations where carcinoma of the stomach is most frequently found. There has been much written in the literature concerning these misplaced intestinal glands. In the newborn the gastric epithelium is not yet differentiated and there is no sharp distinction between gastric and intestinal epithelium. Some investigators are of the opinion that these islands of the intestinal mucosa which we find in later life are derived of the undifferentiated gastric epithelium. A second group of authors maintain that the intestinal islands are the result of metaplastic changes. I believe that the latter conception is less well founded than the former. The gastric epithelium is more highly differentiated than the intestinal epithelium, and a reversion to a lower type of epithelium would be quite improbable. I believe that these islands of intestinal epithelium are congenital and that they are of some significance in the consideration of the etiology of carcinoma of the stomach.

Under the heading of acquired conditions which are related to the etiology of gastric carcinoma, we must consider inflammation and peptic

ulcer. Every case of carcinoma of the stomach has a gastritis, the degree of the inflammation of the mucous membrane varying somewhat. The gastritis usually is atrophic in character and is most marked in the immediate vicinity of the tumor, disappearing distalward. Is the gastritis primary or secondary? In many instances, I feel that it is secondary to the tumor and this holds true, especially for the atrophic type. To a certain extent, however, inflammation is important as an etiological factor, particularly the hypertrophic form. In this condition the folds and rugae of the mucosa are exaggerated, sometimes to the extent that they can be seen in the x-ray picture. From chronic hypertrophic gastritis to the development of polypi is only a step. Polyposis of the stomach is quite frequent. How often do we find carcinoma and polyposis associated with each other? The statistics which I shall quote in this instance and throughout the paper are based on 100 cases of gastric carcinoma autopsied in this hospital. In only 7 per cent of the cases did we find polyps. It is possible, however, that as the tumor grows the polypi are enveloped in the overgrowth and thus obscured. In 4 cases we found an early carcinoma starting in a polyp. I mention all these factors to show you that there are several conditions to be considered in the etiology of carcinoma of the stomach.

Carcinoma of the stomach has been frequently related to peptic ulcer. The surgeon reports a high percentage of malignant transformations of peptic ulcer (up to 70%), while the pathologists report only of from 2 to 5 per cent. In my opinion, the average number of ulcers which become malignant corresponds with the latter figures. In our series, we had only one clear-cut case of carcinoma arising in a peptic ulcer.

I cannot discuss every feature of carcinoma of the stomach; I will confine myself to the following points: (1) the gross appearance of the lesion; (2) its microscopic appearance; (3) the method of local spreading; (4) the distant metastases; and (5) the complications.

In describing the gross appearance of the lesion, we can distinguish 3 main forms: (1) ulcerating; (2) fungating; and (3) diffuse. This classification is important, especially to the surgeon.

The most common form of gastric carcinoma is the ulcerative one. In our 100 cases, 58 per cent were of this variety. Of the ulcerative variety, I distinguish 2 types: (a) the type in which the lesion is sharply demarcated from the normal gastric mucosa; (b) the group in which the lesion has sloping edges which pass gradually into the normal gastric mucosa. In this latter type the carcinoma extends far beyond the edges of the tumor, and the resection must, therefore, be as radical as possible. The surgeon should outline, therefore, the periphery of the tumor. If the edges are sharply demarcated, the resection need not be so extensive as in the case where the edges are sloping.

The fungating carcinoma or cauliflower-like tumor, comprises about 20 per cent of the cases. This type shows less tendency to infiltrate the wall of the stomach than the ulcerative type. Hence, in resecting a fungating carcinoma, the resection does not need to be as radical as in the former type.

Together, the ulcerative and fungating types comprise 78 per cent of our cases. The remaining 22 per cent are diffuse carcinomas. In these cases, large portions of the stomach wall are infiltrated, and there is no circumscribed tumor mass. The diffuse carcinomas fall into three groups. The first is the medullary type in which the wall of the stomach is thick and soft and the different layers of the wall cannot be differentiated. Ulcerated areas are practically always present. The second type is the scirrhous type in which the wall of the stomach is firm and cartilaginous in consistency, and the viscus is shrunken. This is the leather-bottle stomach. I have seen cases in which the stomach had shrunken down to the size of an apple. In this type we find the wall of the stomach thickened but the layers are clearly distinguishable. The submucosa is prominent and the muscularis is hypertrophic and is traversed by fibrous strands. Whereas, the diffuse medullary carcinoma produces extensive metastases, in the scirrhous type metastases are often absent or scanty. The third type is the linitis plastica. Practially all the cases of linitis plastica are carcinomatous in nature. In these cases there is such a luxuriant overgrowth of connective tissue that the tumor cells are difficult to find, and inconspicuous, since they are embedded by so much fibrotic tissue. For this reason some authors doubt the existence of a true linitis plastica. I have seen cases of

typical linitis plastica with metastases, particularly to the rectum, and I feel that practically every case of this kind is a carcinoma with an extensive fibro-plastic reaction (*carcinoma fibrosum*).

As to the location of the lesion, 34 per cent of our cases were in the region of the pylorus, and 29 per cent on the lesser curvature. This makes 63 per cent involving the pyloric region and lesser curvature. The remaining 37 per cent were distributed as follows: greater curvature 15 per cent, fundus 11 per cent, and cardia 11 per cent.

A few words should be said about the histological picture. I mention this because so much is written in the literature about classification or gradation of malignant tumors. The histological classification is based upon the relation between tumor cell and stroma and morphology of the tumor cell. If the stroma grows at about the same rate as the epithelium, a glandular arrangement is maintained and we call the tumor a malignant adenoma. If the stroma lags behind the epithelial proliferation, an adenocarcinoma results. If the reaction of the stroma is scanty and the epithelial cells multiply luxuriously, the tumor is alveolar in character. This type is also known as an encephaloid carcinoma or a medullary carcinoma, and is very malignant. Predominance of the stroma leads to the carcinoma simplex and scirrhus.

How does a carcinoma spread in the stomach? It spreads chiefly in the submucosa along the lymph vessels. The tumor cells may then break back into the mucosa and invade the normal glands. The literature contains many pictures intended to illustrate the carcinomatous transformation of a normal gland. I interpret these pictures to mean that the tumor cells have broken into a normal gland. Where the groups of tumor cells reach the surface of the mucosa, one finds little whitish specks. Thus, a carcinoma of the stomach, may, metastasize to the stomach (e.g., a carcinoma of the pyloric region to the cardia).

The consideration of metastases is very important, because the operability of the case depends largely on it. Sixty-seven per cent of our cases showed metastases to the regional lymph nodes. A few words should be said about the regional lymph nodes. The stomach drains into all of the lymph nodes around the large arteries in the upper abdomen. The lymph nodes along the greater and lesser curvature of the stomach become involved first. At the cardia on the left and right side are two groups of lymph glands which are very early affected. The metastases follow the left gastric artery along the lesser curvature and the gastro-epiploic artery along the greater curvature. Metastases along the hepatic artery lead to involvment of the lymph nodes at the hilus of the liver. Thus the peribiliary lymph nodes are often affected. Metastases along the splenic artery lead to involvement of the peripancreatic nodes. Metastases to the glands around the celiac axis leads to involvement of the cysterna chyli and then the thoracic duct. From the thoracic duct the metastases spread to the tracheobronchial, deep cervical and axillary glands. From the celiac axis, which is in the center of the lymphatic system of the abdomen, metastases may also spread to the iliac lymph nodes. Because of this extensive systemic involvement of the lymph glands, I have seen cases which were diagnosed as lymphatic leukemia. In some instances the inguinal lymph nodes were as large as a fist.

The question of metastases leads us to the complications of carcinoma of the stomach, because many of the complications are due to metastases.

I have already mentioned early involvement of the glands around the hepatic artery and around the hepatoduodenal ligament. The metastases may compress the portal vein and splenic vein and break into them causing thrombosis of these veins. An anemic patient with a carcinoma of the stomach, may come to the doctor complaining of his huge abdomen and ascites, and a large spleen may be found upon physical examination, suggesting a splenic anemia or Banti's disease.

Another complication is the compression of the common ducts by metastatic glands at the hilus of the liver. We found icterus in 6 per cent of our cases. There is no relation between the size of the metastases to the liver and the degree of jaundice. I have seen a case in which a lymph node broke into the common duct and gave rise to an intracanalicular spread of carcinoma.

Another interesting complication arises from metastases around the cardia. A large lymph node at the cardia may break into the stomach at that point and produce a huge ulcer. This may

give rise to the symptoms and x-ray findings of a carcinoma of the cardia.

Second in frequency to the metastases to the regional lymph nodes are the metastases to the liver. We found metastases to the liver in 36 per cent of our cases.

Another type of metastases is the carcinomatous lymphangitis. The involved lymph vessels are thickened, whitish, and firm. Microscopically we find the lymphatics filled by carcinoma cells. A carcinomatous lyphangitis may give rise to an intestinal obstruction in the following way: the connective tissue shrinks about the tumor cells. When the involvement of the lymphatics of the mesentery approaches the mesenteric border, a nodule is formed. Shrinking in this region may cause kinking of the bowel, and hence there may occur an intestinal obstruction.

Another complication is perforation peritonitis. This occurred in 9 per cent of our cases as compared to a frequency of 20 per cent in cases of gastric ulcer. Of these 9 cases, 6 broke directly into the peritoneal cavity and caused a diffuse suppurative peritonitis. In two cases, a subdiaphragmatic abscess on the left side was found. One of these abscesses broke through the diaphram into the left lower lobe of the lung, while the other one broke into the transverse colon. In the 9th case the perforation occurred into the lesser peritoneal cavity, with the formation of a huge abscess posterior to the stomach.

Carcinoma of the stomach may metastasize anywhere. I frequently found metastases to the bones. These metastases may be so marked that they are visible on the x-ray plate, and may cause spontaneous fractures. When we make a systematic histological examination of the bones we find metastases to the bones, especially the bodies of the vertebrae, in 70 per cent of the cases. Most of these metastases are small and insignificant. We have often seen metastases to the pleura from the glands at the hilus of the lungs, and hematogenous metastases to the lungs themselves. Furthermore, metastases may occur to the adrenals and to the kidneys. Five per cent of our cases had metastases to the spleen. In women, carcinoma of the stomach tends to produce metastases to the ovaries. The ovarian metastases are bilateral, and the diffusely infiltrating form of these metastases with mucus producing cells is known as "Krukenberg tumor." In the male, metastases to the seminal vesicles are relatively common.

Another complication is ascites. We found it in 10 per cent of our cases. In 4 cases it was chylous. The ascites is due either to (1) portal thrombosis; (2) generalized carcinomatosis of the peritoneum; or (3) cachexia.

The majority of our cases were quite cachectic. However, from time to time, we observe a carcinoma of the stomach in a well-nourished individual. In these cases the lesions usually are not ulcerated and do not cause obstruction. One, therefore, must not always rely on the weight of the individual in making a diagnosis. Cachexia is due to obstruction and ulceration.

In 4 cases we saw a terminal endocarditis, and in 2 cases there was a suppurative pericarditis. Severe anemia in carcinoma of the stomach is common and it may resemble "pernicious anemia." It sometimes occurs that the lesion in the stomach is small causing no symptoms, and that the blood picture is so marked, that a diagnosis of pernicious anemia is made. These patients, however, do not have the yellow waxy color of the skin which is typical of pernicious anemia, and the icterus index of the plasma is within normal limits.

We must try to correlate the clinical findings with the anatomical observations. Pain is usually severe in the ulcerated form. Obstruction causes most of the symptoms. Blood in the feces on a meat-free diet is tremendously important, even when the x-ray findings are negative. Extensive hemorrhages are rare. In our material, 33 per cent of the peptic ulcers of the stomach died from hemorrhage, while only 2 per cent of the carcinomas of the stomach had fatal hemorrhages. Neither was due to the carcinoma of the stomach primarily. One was due to dilatation of the esophagus, associated with ulceration and erosion of a blood vessel in the floor of the ulcer. In the second case there was a metastases to a perigastric lymph node which had eroded the stomach wall and one of the gastric arteries. Achlorhydria, so common in the advanced stages, not seldom is absent in the early stages. The absence of free acid is due to the complicating gastritis. The finding of lactic acid is very important. If the test is done carefully and repeatedly, lactic acid will be found present in a large per cent of the cases. One can be quite sure of

the diagnosis of a carcinoma "when it is found." There is no relation between ulceration and the presence of lactic acid. Even where the lesion was small, lactic acid was frequently found. I do not think that the presence of lactic acid depends upon acid-producing bacteria or pyloric obstruction. We must remember that carcinoma cells have a metabolism of their own, and that the occurrence of lactic acid may be due to the abnormal metabolism of the tumor cells.

Conclusion

An analysis of 100 cases of carcinoma of the stomach was presented. The etiology, types, frequency and complications were discussed.

SEMINARS

Schedule of meetings and lectures held during the Fall Quarter of 1948, on Wednesday at 1:00 P.M., in Amphitheater A.

October 6—"Coccidiomycosis." Illustrated with Kodachrome lantern slides. Dr. J. D. Kirschbaum, Pathologist, Kern General Hospital, Bakersfield, California.

October 22—"Sludged Blood." Illustrated with color, 16 mm. silent motion picture. Dr. W. H. Knisely, Professor and Head of the Department of Anatomy, University of South Carolina Medical School.

October 27—"Thyroid—Gonad Relations in the Development of Secondary Sexual Characters." Dr. B. B. Blivaiss, Instructor in Physiology and Pharmacology, The Chicago Medical School.

November 3—"Manufacture and Uses of Vitamin D." Dr. W. Dasler, Assistant Professor of Biochemistry, The Chicago Medical School.

November 10—"The Human Thumb—A Phylogenetic Index of Man's Development." Dr. D. A. Willis, Associate Professor of Surgery, The Chicago Medical School.

November 17—"The Pharmacology of Bacterial Toxins." Dr. G. Cantoni, Senior Cancer Research Fellow and Research Associate, Department of Biochemistry, University of Illinois Medical School.

November 24—"Psychiatry as a Biodynamic Study." Dr. H. H. Garner, Professor and Head of the Department of Neurology and Psychiatry, The Chicago Medical School.

December 1—"Pathological Aspects of Nutritional Diseases." Dr. C. L. Pirani, Chief, Pathology Division, Army Medical Nutrition Laboratory, Chicago.

December 8—"Prolonged Labor." Dr. S. J. Turner, Assistant Professor of Clinical Obstetrics, The Chicago Medical School.

POST-GRADUATE SEMINARS

October 6—"Coronary Disease, Diagnosis and Management." Dr. Harry J. Isaacs, Professor and Chairman of the Department of Medicine.

October 13—"Heart Failure; Its Causes and Treatment." Dr. Peter Gaberman, Associate Professor of Medicine.

October 20—"Common Electrocardiographic Abnormalities." Dr. Herman N. Kamin, Associate Professor of Medicine.

October 27—"Occupational Dermatoses Confronting the General Practitioner." Dr. Maurice Oppenheim, Professor and Chairman of the Department of Dermatology and Syphilology.

November 3—"Medical Disease of the Kidney." Dr. Isadore M. Trace, Professor of Clinical Medicine.

November 10—"Peptic Ulcer, Diagnosis, Complications, and Therapy." *Surgical Aspects*—Dr. Siegfried Strauss, Associate Professor of Clinical Surgery; *Medical Aspects* — Dr. Frank Neuwelt, Assistant Professor of Clinical Medicine.

Novembr 17—"Jaundice; Differential Diagnosis." *Surgical Aspects*—Dr. Louis W. Shabat, Assistant Professor of Surgery; *Medical Aspects* —Dr. Martin M. Kirshen, Associate Professor of Clinical Medicine.

December 1—"The Diabetic in Your Office." Dr. Isadore M. Trace, Professor of Clinical Medicine.

December 8—"Heart Disease; How to Determine the Therapy of Choice." Dr. Nathan Flaxman, Associate in Clinical Medicine.

December 15—"Chronic Non-Tuberculosis Diseases of the Lungs." *Surgical Aspects*—Dr.

Saul A. Mackler, Assistant Professor of Thoracic Surgery; *Medical Aspects*—Dr. Charles Berkowitz, Associate in Clinical Medicine.

December 22—"Psychosomatic Medicine."
Surgical Aspects—Dr. David A. Willis, Associate Professor of Surgery; *Medical Aspects*—Dr. Harry H. Garner, Professor and Chairman of the Department of Neurology and Psychiatry.

January 5—"Cryptogenic Febers." Dr. Harry J. Isaacs, Professor and Chairman of the Department of Medicine.

January 12—"Bronchial Asthma; Allergic Aspects." Dr. Abe L. Aaronson, Assistant Professor of Clinical Medicine.

January 19—"Common Problems in Allergy." Dr. Abe L. Aaronson, Assistant Professor of Clinical Medicine.

January 26—"A Critical Analysis of the Hemorrhages in Obstetrics.' Dr. Egon W. Fischmann, Professor and Chairman of the Department of Obstetrics and Gynecology.

February 2—"A Discussion of the Causes and Treatment of Prolonged Labor." Dr. Egon W. Fischmann, Professor and Chairman of the Department of Obstetrics and Gynecology.

February 9—"Functional Bleeding and Gynecological Endocrinology." Dr. Egon W. Fischmann, Professor and Chairman of the Department of Obstetrics and Gynecology.

February 16—"A Resume of the Cancer Problem in Women." Dr. Egon W. Fischmann, Professor and Chairman of the Department of Obstetrics and Gynecology.

February 23—"Carcinoma of the Colon and Rectum; Diagnosis and Treatment." Dr. Earle I. Greene, Professor of Surgery.

March 2—"Intestinal Obstruction." Dr. Allan E. Sachs, Assistant Professor of Surgery.

March 9—"Tumors of the Breast, Diagnosis and Treatment." Dr. Joseph T. Gault, Associate Professor of Clinical Surgery.

March 16—"Treatment of Varicose Veins." Dr. Allan E. Sachs, Assistant Professor of Surgery.

March 23—"Peripheral Venous Diseases; Phlebitis, Thrombosis, Embolism, with Special Reference to the Post-Phlebitic Syndrome." Dr. Leo Zimmerman, Professor of Surgery.

March 30—"Peripheral Arterial Disease; Methods of Evaluating Peripheral Circulation and Recent Advances in Therapy." Dr. Donald S. Miller, Professor and Chairman of the Department of Orthopedic and Traumatic Surgery.

April 6—"The Changing Picture of Thyroid Disease." Dr. Leo Zimmerman, Professor of Surgery.

April 13—"Backache." Dr. Donald S. Miller, Professor and Chairman of the Department of Orthopedic and Traumatic Surgery.

April 20—"Regional Enteritis."
Surgical Aspects—Dr. A. Strauss, Senior Attending Man in Surgery at Mount Sinai Hospital (by invitation); *Medical Aspects*—Dr. Martin M. Kirshen, Associate Professor of Clinical Medicine.

April 27—"Ulcerative Colitis."
Surgical Aspects—Dr. A. Strauss, Senior Attending Man in Surgery at Mount Sinai Hospitall (by invitation); *Medical Aspects*—Dr. Martin M. Kirshen, Associate Professor of Clinical Medicine.

May 4—"Chemical and Metabolic Disturbances of the Blood." Dr. Donald H. Atlas, Assistant Professor of Medicine.

May 11—"Diagnosis and Treatment of Genito-Urinary Emergencies." Dr. Harry C. Rolnick, Professor and Chairman of the Department of Genito-Urinary Surgery.

May 18—"Diagnostic Significance of Hematuria." Dr. Harry C. Rolnick, Professor and Chairman of the Department of Genito-Urinary Surgery.

May 25—"Recent Advances in the Control of Contagious Disease of Children." Dr. Maxwell P. Borovsky, Professor and Chairman of the Department of Pediatrics.

June 1—"Erythroblastosis Foetalis." Dr. Israel Davidsohn, Professor and Chairman of the Department of Pathology.

June 8—"Meningitis in Children." Dr. B. M. Levin, Associate Professor of Pediatrics.

June 15—"Coeliac Syndrome in Children." Dr. Philip L. Aries, Professor of Pediatrics.

June 22—"Causes and Treatment of Hypertension." Dr. Piero P. Foa, Associate Professor of Physiology and Pharmacology, and Associate in Clinical Medicine.

June 29—"Fungus Diseases of the Skin." Dr. David Cohen, Associate Professor of Dermatology and Syphilology.

Book Review

"Infant Nutrition" by P. C. Jeans, A.B., M.D. and William McKim Marriott, B.S., M.D. Fourth edition, 516 pages. The C. V. Mosley Company, St. Louis, Mo. 1947.

(Reviewed by Morton Josephson)

To quote a statement from the preface: "It is the purpose of this book to summarize present-day knowledge concerning the nutritional requirements of infants under normal and pathological condtions, and to indicate the effects of failure to meet any or all of these requirements." This remark and another quote from the preface, "that the fundamental facts concerning the nutritional requirements of infants are now fairly well established, and the most that any type of feeding can accomplish is to fulfill these requirements," approximately outline the scope of this work.

The book may be divided into three parts. There is a section concerning the fundamentals underlying growth, development, metabolic, and digestive processes; another is devoted to the considerations entailed in feeding normal infants; and a third involves a discussion of a variety of pathologic conditions that are related to infant nutrition.

In the first part, salient facts of physiology and biochemistry considered essential to the intelligent construction of an infant's diet are discussed. There is a brief account of the factors involved in energy metabolism. And in broad strokes, the biochemistry and physiology of carbohydrates, proteins, fats, vitamins and inorganic constituents are considered, as well as the processes involved in the phenomenon of digestion. There are frequent applications, here alluded to, concerning particular feeding problems. And space is allotted to the average growth and development values of the normal infant as a gauge to the efficacy of a feeding program.

The segment of the book devoted to normal feeding is a comprehensive report of a multitude of factors involved in breast feeding, in the providing of artificial milk, and in the progressive construction of the infant's diet as he develops. The composition of human milk, the contra-indications of breast feeding, the hygiene of the nursing mother, techniques of breast feeding, mixed feeding, weaning, requirements of a satisfactory artificial feeding, the problem of bacterial contamination, the constituents of cows' milk, the various types of artificial milks, construction and preparation of formulas, additions to the diet such as cod liver oil, orange juice, vegetables, fruit, cereals, and meat, and several other topics are discussed. There is here gathered a collection of material of considerable practical value, and a study of this portion of the book equips the reader with information necessary to cope with the various exigencies that may arise in planning a diet and guiding an infant's development.

In the third portion of the book a good deal of infant pathology is broached. The chief gastrointestinal disturbances of the infant, vomiting, diarrhea and constipation receive considerable attention. The reciprocal relationship of infection to nutrition is discussed, and the importance of chemical pathology of the body as related to feeding and nutrition is dealt with in the chapters on anhydremia, acidosis and alkalosis, ricketts, and tetany. Also considered are the topics of malnutrition, prematurity, allergy, coeliac disease, and therapeutic techniques such as blood transfusions and gavage. Within some of these general headings are included intussusception, plyoric stenosis, atresia of the esophagus, otitis media, syphilis, and tuberculosis. And as much space is devoted to etiology, pathology, symptoms, diagnosis and treatment as to the nutritional factors involved. This last portion of the book, therefore, simulates a short compendium of infant diseases. For many pathologic conditions of the infant will effect his nutritional processes. and the authors apparently felt that any condition at all related to nutrition is deserving of consideration.

PROTEIN STRUCTURE AND FUNCTION

By DR. LEO J. SAIDEL, Ph.D.

Department of Biochemistry of The Chicago Medical School

THERE are, generally speaking at least two different approaches to the problem of protein structure. One approach is what might be called the classical approach of the organic chemist. When applied to any ordinary organic compound, this consists of a series of logical steps somewhat as follows. It is necessary, first, to determine the purity of the compound; second, to obtain an ultimate analysis and an estimation of molecular weight to conform with whole number relationships between the constituent elements; third, to identify characteristic groups or radicals qualitatively; and subsequently, quantitatively. With this information it is usually possible to formulate one or more skeletal structures which may be identified experimentally by various methods, such as decomposition reactions. Once the basic skeleton is established, it is then possible to postulate several formulae which account for all of the properties of the substance, one of which formulae may be verified by synthesis. This then, may be considered the approach of the organic chemist to the problem of determining the structure of any relatively simple organic substance.

However, proteins are definitely not simple organic substances. After approximately 125 years of study we are still a long, long way from the synthesis of a biological protein. In recent years, several new techniques, which depart considerably from the traditional organic approach, have been applied to this problem. These may be lumped together as methods of physical chemistry. They include for the determination of molecular weight such techniques as: 1) measurement of osmotic pressure; 2) measurement of diffusion rates; 3) measurement of sedimentation velocity and sedimentation equilibrium in the ultra-centrifuge; 4) x-ray study of crystal form; and 5) surface measurement of mono-molecular films. For the study of the shape of the protein molecule there are: electron microscopy, with or without the gold shadowing technique; and double refraction of flow. For the study of overall patterns within the molecules there is x-ray diffraction. Finally, for the purification and characterization in terms of charge distribution, there is electrophoresis.

I apologize for merely listing these methods, with no word of explanation, but the problem of protein structure is so large in scope, that I must necessarily limit the discussion to certain phases of it with which I am more familiar. Consequently, I shall consider primarily the contributions which the organic approach has made to this problem.

As indicated previously, when an organic chemist is confronted with the problem of working out the structural formula of a new substance, the first thing he is concerned with is purity. Is he dealing with a single molecular species, or with two or more different molecular species? This, in itself, presents quite a problem to the protein chemist, and a most important one, because everything else must rest upon it. Obviously, before the formula of a substance can be determined, it is necessary to know if one is dealing with a *single* substance. But does this concept exist, in a practical sense, when dealing with proteins? Is it possible to isolate a workable quantity of a single molecular species of a protein, or do proteins, as we know them, rather exist as a whole spectrum or distribution of compounds having similar properties reflecting an approximately similar chemical constitution? In other words, when we refer to proteins must we keep the diagram of a probability curve in the back of our minds, and think of the most probable properties, and the most probable constitution?

Such an idea, although, I admit, repugnant, cannot be dismissed too lightly. Such criteria of purity as sedimentation in an ultracentrifugal field, or electrophoretic mobility, or crystallizability, which are commonly used by the protein chemist, are inadequate, when considered singly. In a molecule as complex as the protein molecule, there are theoretically millions of possible distributions of atoms, all of which will have identical molecular weights. Similarly, it is quite possible for different compounds to have the same mobility in an electric field, although there is

less likelihood of the mobilities being the same at several different pH's. However, such studies together with phase solubility studies, immunological studies, and amino acid composition studies, when considered together, *do indicate* that it is possible to speak about homo-molecular proteins. Nevertheless, it is well to keep in mind that many so-called pure proteins, such as egg albumen, lactalbumen, and perhaps even insulin, may actually be mixtures of two or more different molecular species,—although they are probably not completely amorphous in the sense discussed above.

It is only recently that *really adequate* criteria for protein purity have been developed, and these largely as a result of the previously mentioned new methods of physical chemistry. Long before pure protein preparations were actually available, organic chemists were attempting to study these substances according to their usual procedures. Probably the first ultimate analysis of proteins, i.e., in terms of the constituent elements, were published by Boussingault (1) and Mulder (2) in 1836, working independently. Shortly after, Mulder and Liebig (3, 4) tried to formulate empirical formulae and minimum molecular weights for these substances, but the problem was not a simple one. The empirical formula, you will recall, is the lowest whole number ratio between the constituent elements, and the minimum molecular weight is the sum of the atomic weights in the empirical formula. The *actual* molecular weight is some integral multiple of the minimum molecular weight.

If one is seeking whole number relationships between the elements of some simple substance like glycine, $C_2H_5O_2N$, one can apply analytical data with considerable confidence regarding the question of whether there are five or six hydrogen atoms in the molecule. This is obvious inasmuch as the difference between five and six is 20%, whereas an error of not more than a few tenths of one per cent is likely to occur in the analysis of the carbon, hydrogen, and nitrogen. But when one is dealing with a substance like B-lacto-globulin, for which the empirical formula is *something like* $C^{1864}H^{3012}N^{468}S^{21}O^{576}$ (5), the analytical data simply isn't sufficiently precise to tell whether the ratio of C to S is 1864/21 or 1865/21. Consequently, the early workers published ridiculously simple empirical formulae for the proteins with molecular weights that had little relationship to those we now believe to be correct. So the ultimate analysis alone did not prove to be very useful in the determination of either the formula or the molecular weight. It was only much later, after the search for larger groups or radicals within the protein molecule had become successful, that the organic approach yielded useful data for the purposes of molecular weight determination.

This search for larger units of structure or radicals within the molecule has occupied organic chemists for the past 125 years, from the discovery of glycine as a decomposition product of gelatin by Braconnot in 1820 (6), through one of the most recent discoveries, that of threonine in casein by Rose and his co-workers in 1935 (7, 8), and up to the present day when the search continues, although we are reasonably certain that all of the major constituents of all the common proteins have been discovered. These radicals are the amino acids. They are all similar in structure, having at least one carboxyl group and one alpha amino or imino group. All of them which occur in ordinary proteins, except glycine, are optically active, and of the L configuration on the alpha carbon. In addition to the amino acids many proteins contain ammonia, phosphoric acid, metals, and various other more complex prosthetic groups such as sugars, lipids, and nucleic acids. I shall confine my discussion, for the most part, to proteins containing only the amino acids and ammonia. Of course, when I state that proteins contain these radicals, I mean that these are the radicals which are liberated by acid or enzyme hydrolysis. More drastic treatment will produce other types of organic compounds from amino acids.

When the organic chemists had gained a fairly complete knowledge of the kind of radicals which constitute proteins—, that is, when they possessed a satisfactory qualitative analysis for proteins, they began to theorize about the way in which these groups were linked together in the molecule.

The Hofmeister-Fisher theory of peptide bond linkage:

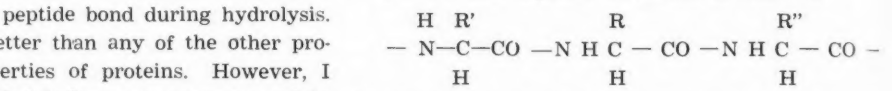
$$\begin{matrix} H & & H \\ R-C- & CO/N & H-C-R \\ NH & & CO \end{matrix}$$

proposed by these men around the turn of the

century (9, 10), has received the widest acceptance, and in this discussion I shall assume that *this* is the principle linkage in proteins. The free amino acids come from the peptide by addition of water to the peptide bond during hydrolysis. This explains better than any of the other proposals the properties of proteins. However, I should mention that it does not appear to explain all reactions. For example, Dr. R. G. Roberts has observed certain reactions in liquid ammonia which are difficult to reconcile with the peptide bond theory (11). This theorizing concerning linkage came, of course, prior to the possession of any precise knowledge of the proportions of the different groups within the molecule, that is, before quantitative amino acid analysis.

However, with the development of accurate methods of analysis for the hydroxy-amino acids serine, and threonine by Nicolet and Shinn in 1941 utilizing a specific oxidation reaction (12, 13, 14, 15), and the partition chromatography methods of Martin, Synge, Tristam, and others in England (16, 17, 18) at about the same time for alanine, valine, leucine plus iso-leucine, phenylalanine, and proline, and most significant, the development of bio-assay methods for all of the amino acids by Lyman, Dunn, Shankman, Snell, Beadle, Gale (19, 20, 21, 22, 23), and others since 1943, it has become possible to perform nearly complete, if not complete, quantitative amino acid analysis for all of the proteins.

The first, and thus far probably like the most complete analysis, was obtained in the laboratory of Dr. Brand at Columbia in 1945 (5). Dr. Brand's analysis of B-lactoglobulin, the principal proteins of cow's milk plasma, was the first serious attempt to account for 100% of the weight of a protein in terms of amino acids. I shall discuss this work in some detail, in order to draw up a precise balance sheet co-ordinating all of the data available, it was necessary to make certain assumptions. First, it was assumed that B-lactoglobulin is a single molecular species in which, consequently, the constituent amino acids occur in integral molar quantities. There is much evidence taken from solubility, ultracentrifugal, electrophoretic, and dissociation studies to indicate that this is so. (However, on the basis of very recent electrophoretic studies at different pH's, the homogeneity of even B-lactoglobulin has been questioned (24).) Secondly, it was assumed that amino acids occur in the molecule in peptide linkage. This is necessary for the precise evaluation of the analytical data. We picture the amino acids linked together in chains as residues



rather than as the free amino acids which occur in hydrolysates.

The residues differ from the amino acids which occur in hydrolysates by one molecule of water, except where they occur at the end of an open chain.

Since an open chain must have a free amino group at one end, and a free carboxyl group at the other end, it is obvious that the open chain must contain an extra molecule of water.

All of the inside amino acids, which means nearly all of them are present as residues and consequently the analysis must be expressed not in grams of free amino acids per 100 grams of protein (as is customary), but as grams of residue amino acids per 100 grams of protein.

The third and last assumption is, that the only amino acid containing a non-alpha amino groups is lysine, which has an epsilon as well as an alpha amino group.

$$NH_2CH_2CH_2CH_2CH_2CHNH_2COOH$$

Consequently, the only free amino groups on the protein molecule are the epsilon amino groups of lysine, and the alpha amino groups which are present at the end of the peptide chain. Any other alpha amino groups are linked in peptide bonds. By deducting the epsilon amino nitrogen of lysine, obtained from an independent lysine determination, from the total free alpha amino nitrogen determined on the intact protein by the Van Slyke procedure, a measure of the free alpha amino nitrogen is obtained. It was assumed that each alpha amino nitrogen was indicative of a peptide chain, thus giving the number of chains occurring in the molecule. This implies that proline, which has no alpha amino groups but an alpha imino group, does not occur at the end of a chain, and also that there is a free carboxyl group for every free amino group.

I will not enumerate the various methods of analysis for all of the amino acids found present,

but values for the percentage of amino acid residues were obtained by various methods, both biological and chemical, for nineteen different amino acids (twenty, if glutamine is included). Hydroxyproline and hydroxylysine were absent. If the analysis were complete, the percentage should have totalled 100.00%. Actually, the sum of the amino acid residues was 99.13%. But expressing all of the amino acids as residues neglects the terminal water present as a result of the free amino and the free carboxyl groups at the end of each chain, as mentioned previously. When this terminal water was calculated and added to the amino acid residues, the total became 99.33%. A further correction, necessitated by stoichiometric considerations, increased the sum to 99.62%.

In addition to the amino acid analysis, an ultimate analysis for sulfur nitrogen, carbon and hydrogen was also obtained from which oxygen was calculated by deducting the sum from 100%. Phosphorus and other elements were absent. Each of these values, which can be determined with considerable accuracy, was then used to check the correctness of the total amino acid analysis. The sulfur containing amino acids are cysteine, cystine, and Nethiorine. The amount of sulfur present in these amino acids was *calculated* and found to be 1.597%. Since the sulfur *analysis* on the protein itself was 1.604%, this provided a good check on the accuracy of the sulfur containing amino acid determinations.

In Table I, I have listed similar comparisons for all the elements.

Table I

Calculated from individual

Amino Acid Analysis	*Ultimate Aanalysis*
Sulfur..... 1.59%	.....1.604%
Nitrogen.....15.58	.....15.60
Carbon.....53.09	.....53.39
Hydrogen..... 7.17	..... 7.22
Oxygen.....21.86	.....22.19

Only the C and O are a trifle low. Of course, the sum of the elements, with the exception of sulfur, obtained from the individual amino acid determinations, is not very sensative to errors in these determinations. It is possible to be off a good bit and still get a pretty fair balance sheet. However, it serves as a check.

We may now ask ourselves: what does such a complete analysis permit us to conclude concerning the structure of protein? Earlier, I indicated that it was possible to calculate the minimum molecular weight from the amino acid analysis data. The arithmetic becomes somewhat involved, but exactly the same principles are employed as are used by any beginner in general chemistry who attempts to establish the formula of a compound from an analysis of the elements it contains.

The percentage data is converted into molar concentrations and then one searches for some single factor which will convert all of the molar concentrations into whole numbers. These whole numbers are the empirical formula, while the sum of the atomic weights is the minimum molecular weight. It is also possible to calculate the minimum molecular weight from the analysis for any single element, once one has determined the whole number of times the element occurs in the empirical formula. In applying this procedure to amino acid data, one substitutes amino acid residues for elements, because the amino acid residues, unlike the elements, occur in small number ratios.

Based on the five most accurately determined constituents, the minimum molecular weight of B-lactoglobulin was found to be 42, 020 = 105, and the empirical formula in terms of amino acid residues:

$Gly_8Ala_{29}Val_{21}Leu_{50}Ileu_{27}Pro_{13}Phe_3CySh_4(CyS\text{-})_8$

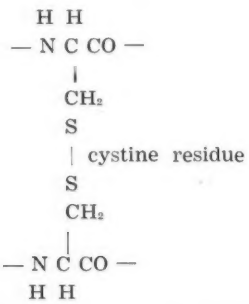
$Met_9Try_4Arg_7His_4Lys_{33}Asp_{36}Glu_{24}(Glu\text{-}NH_2)_{32}$ Ser_{20}

$Thr_{21}Tyr_9(H_20)_4$ — using Dr. Brand's symbols for the amio acid residues. (5) There are a total of 370 amino acid residues in the molecule. The minimum molecular weight as determined by analysis, agrees very well with the best value obtained with the ultracentrifug, 41, 600:—which indicates that the minimum molecular weight is also the actual molecular weight.

The precise way in which the data checks itself is also a strong indication that the first two of the initial assumptions concerning structure were correct. Thus, the fact that it is possible to express all of the amino acids as whole number ratios on the basis of a molecular weight, which is in excellent agreement with the molecular weight found by other methods, indicates that B-lactoglobulin is a homomolecular species. The data can also be construed as strong evidence

in favor of the important role of the typical peptide linkage, which was the basis for all of the calculations. The fact that these arguments may be true for a typical protein like B-lactoglobulin, makes it highly possible that they are generally true for all proteins.

If the assumptions regarding the free alpha amino nitrogen are justified, then it would be possible to conclude that B-lactoglobulin has four open chains in the molecule joined by some, as yet uncertain, non-peptide linkage. These sub-units, as they may be called, could not all be identical, because the minimum molecular weight and the actual molecular weight, as determined by other methods, are the same. If the sub-units were identical, then the minimum molecular weight would be 1/4 of the actual molecular weight. It is possible that the four disulfide groups in the molecule could link the sub-units, but there is, as yet, no evidence that this is actually so.



One almost has to conclude that any disulfide groups present must link peptide chains, but, of course, they do not have to be open chains.

In starting to speak of sub-units of protein structure, one leaves the realm of reasonably certain knowledge and enters the realm of conjecture and theory. Although it is no longer too difficult to give molecular weights, and empirical formulae for proteins, and there is now rather good agreement on the predominant linkage in the protein, one must proceed very tentatively on further details of structure. A good beginning has been made, or, I should say, many beginnings have been made. Unfortunately, thus far, these beginnings do not appear to converge at very many points.

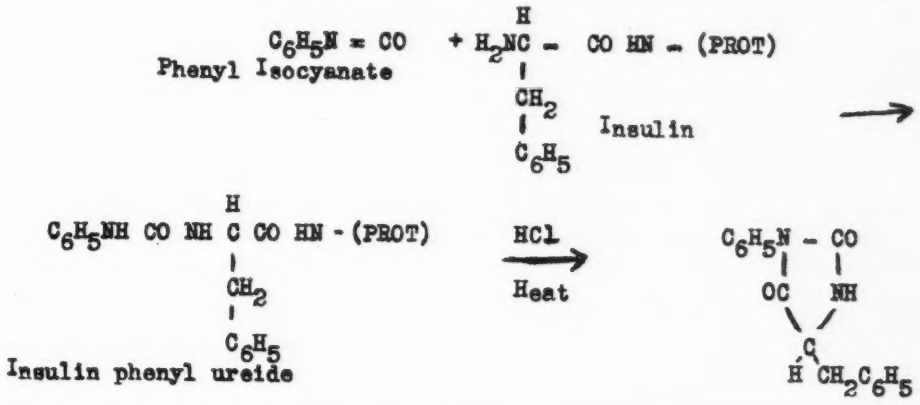
The presence of free alpha amino groups and disulfide groups in some proteins leads us to expect some sort of sub-units. The organic chemist should then be able to split the molecule into these sub-units, separate them, and study their properties. Attempts to do this have not been very successful thus far. The point of attack is usually the disulfide bond. The hormone insulin possesses a great many of these linkages. Just within the last year, Sanger (25), a British worker, completely oxidized the cystine residue in insulin to cysteic acid by means of performic acid, and then studied the product electrophoretically. This showed the presence of three new components. By neutralization he was able to separate the product into two fractions of equal weight, the solution containing mainly glycyl terminal residue; the precipitate mainly phenylalanyl terminal residues. There are several other ways in which peptide chains might plausibly be linked together. For example, they might form salt linkages between the omega carboxyl groups of the dicarboxylic acids and the epsilon NH_2 groups of lysine. Again, they might possibly be held together through hydrogen bonding. There is, however, little evidence for these other types of linkage, with the possible exception of the fact that native proteins, such as insulin, will dissociate into sub-units under very mild conditions.

Regarding the fine structure within a single peptide chain, that is, the order or sequence of amino acids and the position of the linking groups within the chain, the organic chemist has said even less. The very active group of workers in England which I mentioned previously, is applying chromatographic methods of separation to partial hydrolysates. The peptide chains are broken down into smaller peptides, which are fractionated chromatographically and indentified, with the hope that the fragments will give clues to the structure of the original chain. With this procedure they have failed to find a periodicity claimed by other workers. They have succeeded in determining the sequence of amino acids in gramicidin-S, which is a small cyclic polypeptide (26). Probably the ideal solution to this problem would involve removal and identification of terminal amino acids from the peptide chain, one at a time, without alteration of the remaining peptides. Actually, such methods are available, but the operations involved are apparently prohibitive. They have not been used extensively, or successfully. However, other methods of identifying only the terminal amino acid of the

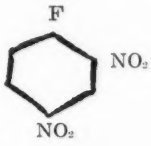
original chain, or of fragments of the chain, are being used with greater success. One of these is the tagging of the terminal amino acid with some non-hydrolyzable reagent, followed by hydrolysis of the chain, and identification of the tagged amino acid. An instance of the successful application of this method is the reaction of insulin with phenyl isocyanate and the isolation of the phenyl hydantoin of phenylalanine in the hydrolysate, by Jensin and Evans (27).

plied to other proteins and to protein-split products.

Other methods for identifying the terminal residues only depend on the different character of peptide bonds at the ends of the chains. Thus, Dakin (29) and later Levine (30) found that while central amino acids were racemized under the influence of alkali, terminal amino acids, which carried a free amino or carboxyl group, remained completely unaltered. The racemiza-

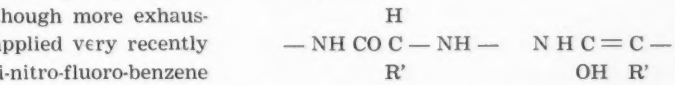


In this way it was determined that one of the terminal amino acids of insulin is phenylalanine. The same type of method, though more exhaustive in its scope, has been applied very recently by Sanger (28). He used di-nitro-fluoro-benzene



which reacts with free amino groups of the protein in the cold, to form the di-nitro phenyl amino acid residue wherever free amino acid groups occur on the molecule. Of course, in this method the epsilon amino group of lysine also enters the reaction. The hydrolyzed protein contains the di-nitro-phenyl amino acids, which can be both separated on the chromatographic column and estimated by virtue of their color. This method was applied to insulin, which he found contained two glycine terminal residues, two phenylalanine terminal residues, and two lysine epsilon groups per sub-unit of 12,000 molecular weight. This very elegant method is being ap-

tion was explained by enolyzation at central peptide bonds.



Presumably, the optically active amino acids in the protein hydrolysate were located at the end of a chain. Finally, much use has been made of enzymes which are specific for a peptide bond next to a free amino or a free carboxyl group. These are used for identifying terminal amino acids (31).

However, to summarize, it is necessary to admit that although sequence of amino acid residues in small polypeptides has been worked out by the above methods, little progress has been made along these lines when dealing with large peptide chains.

Although the chemists have only vague notions about what might be called a two-dimensional representation of the protein molecule—that is, the sequence of amino acids in the chains, the sequence of chains in the protein, the point of linkage between chains, etc.—they have, nevertheless, attacked the problem of the three-dimen-

sional configuration of the protein with considerable vigor. By three-dimensional figuration I mean the manner in which these huge peptide chains roll themselves up, or wrinkle up, within the molecule by reason of cohesion forces by which the various parts of the peptide chain attract each other.

That they do roll up is known, simply because they may be unrolled and spread out. This spreading out is what is generally meant when one speaks of the denaturation of a protein. The ways in which this change is detected, and the study of the change, lies largely within the province of the physical chemist, who uses such methods as X-ray diffraction, measurements on protein films, surface measurements of viscosity, diffusion, and sedimentation. It is on such studies as these that the specific three-dimensional representations of proteins by Astbury (32), by Pauling and Mirsky (33), and by Wrinch (34) have been based. The organic chemist has tried to use these structural ideas to explain the different chemical properties of native and denatured proteins — the change in the digestibility by enzymes, the loss of oxygen-combining powers of hemoglobin, the increased reactivities of groups within the protein molecule such as the sulfahydryl, the disulfide, and the tyrosine groups.

For example, native egg albumin is quite soluble at its iso-electric point; it is resistant to proteolytic enzyme action; it does not give characteristic tests for the sulfhydryl group such as the nitro prusside test and reduction by various mild oxydizing reagents. However, when egg albumin is denatured by heat as determined by insolubilitity at the iso-electric point, it then suddenly becomes much less resistant to proteolytic digestion, and manifests all the usual tests for sulfhydryl groups. Many leading workers in the field believe that these phenomena can be explained by what they call the accessibility theory. They theorize that the native protein is rolled or coiled up, making certain groups in the interior of the molecule inaccessible. When denaturation occurs the molecule opens up, rendering these interior groups accessible. The exposure of polar groups causes the molecules to clump together and precipitate. Peptide linkages, which can be attacked by proteolytic enzymes, are exposed, similarly chemically reactive groups such as the sulfhydryl group make their appearance. This theory, although unacceptable to other leading workers in the field, has been of great value because it has stimulated, and continues to stimulate, much research (35, 36).

I have tried to present a very sketchy review of our present knowledge of protein structure, primarily in terms of amino acid make-up.

Now I should like to consider briefly what the knowledge of protein structure can ultimately contribute to our understanding of biological mechanisms.

Specifically, what significance does the presence of particular amino acids in certain definite proportations and arrangements in proteins such as pepsin or insulin, for example, have with reference to the activities of these proteins? If amino acids could be added or subtracted at certain points in the chain, interchanged, or modified chemically, what would happen to the activities? Is the entire molecule functional, or is it only part of it? Where a protein appears to have several different functions as insulin, for example, or different activities in different environments, as the viruses, would it be possible to identify the different activities with different parts of the molecule and to separate them? More indirectly, what is the *actual mechanism* of biochemical catalysis, of antigen-antibody reactions, of anti-body formation? What is the mechanism of orderly gene duplication, of uncontrolled duplication, of failure to exactly duplicate? What is the mechanism of protein synthesis in general? These are some of the questions which a knowledge of protein structure and of protein chemistry, which will come with the elucidation of structure, will perhaps answer. I shall mention only two directions which work in this field has taken. First, chemists are trying to observe what happens to biological activity when proteins are modified (37); second, they are trying to correlate differences in the quantative analysis of a series of belated or unrelated proteins with differences in biological activities.

The first direction may be illustrated by the following examples: Pepsin may be progressively inactivated by acetylation of its phenolic and free animo groups. Activity may be restored by removal of these acetyl groups. When the more easily removable acetyl groups on the tyrosine residues are hydrolyzed, leaving all of the free amino groups still bound, the protein retains all

of its original activity. This indicates that the free amino groups of pepsin, whether they come from lysine or terminal amino acids, are not essential for enzymatic activity, but that the phenolic groups of tyrosine must be free (38, 39). Similar studies on urease (40, 41, 42) indicate that it has two kinds of sulfhydryl groups, the first kind gives a nitro-prusside test and can be readily oxidized by porphyrindin without an effect on the activity of urease. Apparently these sulfhydryl groups are unessential for activity. Sulhydryl groups of the second kind, perhaps differently situated on the urease molecule, do not give a nitro-prusside test, and require a stronger oxidizing agent — mercuribenzoate — to oxidize them. However, the oxidation of these sulfhydryl groups destroys the activity . . . although activity may be restored with cysteine. With insulin, as with pepsin, acetylation studies show that while free amino groups are not essential for hypoglycemic activity, the tyrosine phenolic groups are essential (43). Further studies indicate that all of the disulfide groups are essential (44, 45, 46), but that neither the aliphatic hydroxyl groups nor the net charge of the protein participate in hypoglycemic activity (47).

The most interesting work, I think, comes from the study of viruses and genes (48), because these proteins undergo changes within their biological environment, which are reflected often-times in strikingly different biological activity. These changes are called mutations. To date, it has not been possible to control them to any great degree. Mutations can be induced in viruses by non-specific changes in environment which produce unidentifiable chemical changes.

An example is the production of the 17D strain of yellow fever by successive passage of yellow fever virus through mouse brain and tissue cultures (49). This modified virus causes an extremely mild form of the disease, which immunizes against the more severe form of the disease caused by ordinary yellow fever virus. This was a chance production of a modified strain which cannot even be reproduced. Beedle, Tatem (22), and others have produced mutations in the mold Neurospora by irradiation with x-rays or ultraviolet rays, and by chemical agents, which are reflected in an altered metabolism of the organism. Specific metabolic reactions appear to be linked to a particular gene. But here again it is impossible to identify the chemical change since it is not possible to study single genes; it may even be that these treatments simply destroy one or more genes responsible for the metabolic reaction. However, it has been possible to produce definite known and reproducible changes in chemical structure of viruses which do not inactivate the virus. Sulfhydryl groups of tobacco mosaic have been oxidized with iodine (50), and acetyl (51) and phenyl ureido (51, 52) derivatives have been prepared by reaction with ketene and phenyl-iso-cyanate, respectively, without changing the specific virus activity qualitatively or quantitatively. Up to 70% of the free amino groups, and 20 to 40% of the phenol plus indol groups of the virus molecule can be covered without significant inactivation. Beyond that, however, the virus loses activity. When these active virus derivatives (the altered preparations) are inoculated into normal Turkish tobacco plants, the disease produced is indistinguishable from ordinary tobacco mosaic disease. But, unfortunately, when tobacco mosaic virus is so isolated from these diseased plants, it is indistinguishable from ordinary unmodified tobacco mosaic virus. In other words, it has been impossible to produce heritable changes in viruses. It is not known whether the groups that are covered, following more drastic treatment, differ qualitatively from those that are first covered.

The activity of viruses has been *modified* by this treatment it has not been simply *destroyed.* This has been proved by inoculation of these tobacco mosaic derivatives into bean plants (53). Ordinary tobacco mosaic virus will grow with a certain specific virus activity in bean plants. When the tobacco mosaic virus derivatives, with unaltered specific virus activity for Turkish tobacco plants are tested on bean plants, they have as low as one-sixth the specific virus activity of ordinary tobacco mosaic virus. In other words, definite known and reproducible chemical changes in the virus molecule result in no change in activity for tobacco plants, but modified activity for bean plants.

The other type of study, that is, the correlation of quantitative analysis of proteins with biological activity, may likewise be illustrated by an example drawn from the virus field (54). A number of related strains of tobacco mosaic virus are known. Quantitative analysis for all of the com-

monly occurring amino acids were performed on a number of them. These analyses, in most cases account for about 98% of the proteins by weight. The killing strain, J14D1, was found to differ from the ordinary non-lethal strain only in its content of glutamic acid and lysine. It is known that strain J14D1 arose from the ordinary strain by *two* successive spontaneous mutations that could be observed. (One cannot be certain that these were the only mutations.) It may be significant that only *two* differences in composition were found. Another strain, HR, is distantly related to ordinary tobacco mosaic virus, and the results indicate that it differs in at least thirteen respects. Included among the differences were significant amounts of the amino acids, histidine and methionine, which the ordinary strain does not contain at all.

Thus, mutations may result in the complete gain or loss of an amino acid. Despite the great differences which exist between members of this series, they all, nevertheless, have particle shapes and sizes that are indistinguishable. Here, for the first time, it was possible to correlate definite changes in chemical structure with mutation.

These studies have been extended to two different strains of influenza virus (55) which, though practically identical in their general physical-chemical properties, are different immunologically. Only five significant differences were found in the analysis for seventeen amino acids.

In conclusion I should like to quote a short passage from the *Gibbs Medal Address*, which Dr. Stanley recently presented before the American Chemical Society (48). Referring to the chemical changes experimentally produced in tobacco mosaic virus, Dr. Stanley says: "It is believed that the present results provide the first example of a modification of virus activity by means of definite, known and reproducible changes in the chemical structure of a virus. They lend encouragement to the belief that eventually heritable structural changes will be achieved in the chemical laboratory. The accomplishment of this objective will represent a feat of major importance. It would carry with it implications of far reaching significance to medicine, biology, genetics, chemistry and philosophy. It is conceivable that virus activity could be used for beneficial purposes, to prevent much human suffering and great economic loss, to probe into the deepest mysteries of life, and to provide knowledge which might affect the destiny of all living things. Certainly, the horizons of chemistry are ever expanding."

* * * * *

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NEVER FORGET YOUR PARENTS

(Popular Ballad)

A young man once was sitting
Within a swell cafe,
The music it was playing sweet —
The people was quite gay.
But he alone was silent,
A tear was in his eye —
A waitress she stepped up to him, and
Asked him gently why.

He turned to her in sorrow, and
At first he spoke no word,
But soon he spoke unto her, for
She was an honest girl.
He rose up from the table
And in a voice replete with tears
In that elegant cafe,
To her he then did say:

Never forget your father,
Think all he done for you;
A mother is a boy's best friend,
So loving, kind, and true.
If it were not for them, I'm sure
I might be quite forlorn;
And if your parents had not have lived
You would not have been born.

A hush fell on the laughing throng
It made them feel quite bad,
For most of them was people, and
Some parents they had had.
Both men and women did shed tears,
The music it did cease,
For all knew he had spoke the truth
By looking at his face.

The waitress she wept bitterly
And others was in tears;
It made them think of the old home
They had not saw in years.
And while their hearts were heavy, and
Their eyes they was quite red,
This brave and honest boy again
To them these words he said:

Never forget your father,
Think all he done for you;
A mother is a boy's best friend,
So loving, kind, and true.
If it were not for them, I'm sure
I might be quite forlorn;
And if your parents had not have lived,
You would not have been born.

—Franklin P. Adams

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I might be quite forlorn;
And if your parents had not have lived,
You would not have been born.

—Franklin P. Adams

School And Faculty Notes

1899

Dr. Daniel Webster Gross, of Worthington, Mass., a graduate of Jenner Medical College, class of 1899, died on November 2, 1947.

1913

On December 29, 1947, Dr. Lambert W. Rosenbaum of the 1913 graduating class of Jenner Medical College, passed away.

1936

The class of '36 will be sorry to learn of the death of one of its classmates, Dr. Fred S. Saruk, on March 14, 1948.

Dr. Jo Rogers Hood has resumed practice after serving in the military forces, and is now located at 118 So. 80th St., Birminigham, Alabama.

1940

It's twin girls, Daphne Jo and Deborah Lee, for Dr. and Mrs. Herman J. Horvitz, born July 7, 1948.

1941

Dr. and Mrs. Edwin I. Hirsh proudly announce the birth of Jean Barbara on April 13, 1948.

1943

Dr. Allen W. Jachman has opened his office for the practice of medicine at 6731 Olmsted Avenue, Chicago, Illinois.

There appeared in the *Illinois Medical Journal*, the October 1948 issue, an article by Dr. Burton J. Winston, entitled, "Additional Obesrvations in Neostigmine Therapy."

Dr. Edward Nissen has moved his offices to 206 Michigan St., Toledo, Ohio.

A son, David Max, was born to Dr. and Mrs. A. H. Barasch on June 28, 1948.

It was a wedding for Miss Lenore Gordon to Dr. Julius Brant on July 17, 1948.

1944

Dr. and Mrs. Sam H. Rosen proudly tell of the arrival of their twin sons, Jerome Stephen and David Allan, on October 19, 1948.

Peter Andrew now adorns the household of Dr. and Mrs. David Friedman. He arrived on last August 1st, in Brooklyn, New York.

Dr. Joseph S. Berman exchanged marriage vows with Miss Betty Alice Sanders on the 29th of August, 1948, in Brooklyn, New York.

1945

Nine-pound Jeffrey Allan was born to Dr. and Mrs. Melvin Smoley on March 26, 1948.

Erica Louise arrived to Dr. and Mrs. Daniel C. Belden on November 20, 1948, in the Bronx, N. Y.

Daniel Halpern, M.D., opened his office at 160 Wadsworth Ave., New York City, recently.

1946

Dr. Eugene H. Rogers sailed via Grace Line on October 8th for Colombia and Venezuela.

Dr. Emanuel Chusid is now serving a residency in psychiatry in the Veterans' Administration in Colorado, and reports that he likes the work very much.

Frank A. Guida, M.D., is now practicing medicine at 1321 Baynton Ave., Bronx, N. Y.

1947

Miss Marcia Zuriff and Dr. Leonard Rothstein were married January 11, 1948, in Baltimore, Maryland.

Dr. Irwin Bluth took Miss Harriet Ruth Shier as his bride on July 29, 1948, in Brooklyn, N. Y.

Mr. and Mrs. J. C. Shively announce the birth of John Cuthbert on last June 22. She is Dr. Normabelle Helmen Shively, a member of the class of 47.

Dr. Donald D. Morrison has opened his offices at 2473 Barley Ave., Buffalo, N. Y.

Dr. Bernard H. Shulman is now located at 19 Madison St., Oak Park, Ill., for the practice of medicine.

1948

Mr. and Mrs. Max Okner announced the marriage of their daughter, Pearl, to Dr. Samuel Weinberg on December 12th, in Brooklyn, N. Y.

Arthur H. Reinitz, M.D., announces the opening of an office at 737 N. Michigan Ave., Chicago.

Dr. John R. Bucar is now practicing medicine in Apple River, Illinois.

It's a boy, Peter Marshall, for Dr. and Mrs. Stanley Beckerman, born September 26, 1948.

Dr. Alice Jean Ferris was married to Mr. Leon Habin on August 6, 1948, in New York City.

The Drs. Caroline Winograd and Harold Brown were married on the 20th of June at the Windermere East Hotel in Chicago.

Miss Sara Steinman and Dr. Sherman C. Fein-

stein exchanged marriage vows on June 22 in Minneapolis, Minn.

Dean Sheinin named the following students as recipient of the annual C. V. Mosby & Co. award: Morris Binder, Harvey Lozman, Wallace L. Salzman, Melvin Leichtling, Patricia Jordon, Howard Wilk, Jesse I. Abrahams, and Caroline W. Brown.

1951

Mr. Claude Udkoff was married on September 19th to Miss Leah Greenberg of Jerusalem, Palestine, in Chicago.

The following members of the class of '51 heard wedding bells recently:

Bertram Carnow and Miss Caryl Taishoff on September 21, 1948.

Jack Kamanetsky and Miss Shirley D. Sylvan on June 21, 1948.

Morris Sanders and Miss Marion Friedman on June 27, 1948.

Future wedding dates have been set by Marvin Moss and Miss Anita Morowitz for March 20, 1949; and Sherwin Lutz and Anette Stein for the same date, March 20.

In the new arrival column, Rita and Michael Pavlo announce that Carol Ann arrived on July 10, 1948.

Engagements in the class belong to Miss Suzanne Allen and Lee M. Widrow, and to Stanley Leithold and Miss Judy Fierer.

* * *

Irving Siegel, M.D.

Dr. Siegel was born in 1907. He received his B.S. and M.D. degrees from the University of Illinois where he was a member of Alpha Omega Alpha and Phi Lambda Kappa. He served his internship at Cook County Hospital and Chicago Lying-in Hospital. Following this he went to Women's Hospital in Detroit for his residency in Obstetrics and Gynecology. From 1933 to 1941 he engaged in private practice and then in May of 1941 he entered the Medical Corps of the U. S. Army as a first lieutenant. He was discharged in 1947 holding the rank of lieutenant-colonel. Dr. Siegel is a Diplomate of the American Board of Obstetrics and Gynecology, a member of the Chicago Medical Society and the Illinois State Medical Society, and a Fellow of the American Medical Association. He published one article on Obstetrics in **The Military Surgeon,** and two articles in **The American Journal of Obstetrics and Gynecology.**

We wish to welcome Dr. Siegel as a full-time assistant professor in Obstetrics at The Chicago Medical School and associate in Obstetrics at Mt. Sinai Hospital.

* * *

PHYSIOLOGY

The United States Public Health Service, Division of Grants and Fellowships, has approved a grant of about $4,000.00 for the continuation of the work on Phosphorylation by Dr. Foa, Dr. Smith, and Miss Weinstein.

OBSTETRICS

An article entitled, "Current Reappraisal of Total Hysterectomy," written by Drs. W. J. Reich and M. H. Nechtow, appeared in the May 5, 1948 issue of the *American Journal of Surgery.*

NEUROANATOMY

Dr. George Clark, Associate Professor of Neuroanatomy at The Chicago Medical School, was the speaker at the Neurological Seminar of Northwestern University Medical School on March 24, 1948. His topic was, "The Lateral Geniculate Nucleus of the Spider Monkey."

DERMATOLOGY

Dr. Maurice Oppenheim was recently elected to membership in the Chicago Dermatological Society, an Honorary Membership of the Society of Physicians of Vienna, and of the Austrian Dermatological Society. Dr. Oppenheim was invited to the Unna Taung in Hamburg to deliver the main report, September 1948.

MEDICINE

Dr. Nathan Flaxman wrote an article on "Digitoxin Poisoning; Report of Thirty Cases," which appeared in the *American Journal of Medical Science,* the August 2nd issue.

OTOLARYNGOLOGY

Dr. Maurice H. Cottle, Professor and Chairman of the Department of Otolaryngology, spoke before the Michigan Triological Society at its meeting in Grand Rapids, on "Surgery of the Nasal Septum in Adults and Children and Its Association with Rhinoplastic Surgery."

DEAN JOHN J. SHEININ

Dean Sheinin was the speaker at the Commencement Exercises at the Mount Sinai Hospital School of Nursing on April 7, 1948. His address was entitled, "Nurse of the Future."

THE VALUE OF BALANCED EXAMINATION IN THE TEACHING OF ANATOMY

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AT THE present stage of our educational development, examinations are considered as the main, if not the sole, source of information for the evaluation of the student's progress in a course and for the issuance of the final grade. This practice is not free of criticism, but criticism is not the purpose of the present paper. Rather, it is to point out that examinations can be put to greater service in education. Examinations can, if properly planned, train the student's mentality, impart a proper method of study, and cultivate the scientific method. Such examinations, I wish to call balanced examinations.

During the last 25 years, I have had the opportunity to be associated with six medical schools at which I had the privilege to study their methods of teaching anatomy to medical students. I have endeavored to study the effect of the methods used at these institutions on the student's understanding and his power of retention of the subject matter. Examinations and re-examinations at more or less definite intervals served as indicators. Some examinations were repeated without previous announcement, three months after completion of the course, some six months, and in some instances, two years after finishing the course. The examinations, of course, were the same as the final examination. The results of state and national board examinations formed part of the data. I also endeavored to ascertain the effect of correlative teaching by instructors of subsequent courses.

The student's ability to understand and retain the materials studied depends on a number of things, some of which are beyond the scope of the present paper. His mental ability is, of course, the major factor. The ability of the teacher and the methods used is undoubtedly next in order. Repetition is next, and for lasting retention, it is very important.

The student's mental ability need not detain us here except for two aspects, which often interfere with the proper spotting of his intelligence, and these are his previously established likes or dislikes for certain courses. The so-called "good" courses and 'bad" courses is a campus tradition, often without any foundation, but play a role in the mastering of the course.

The claim often heard that a good teacher is one who knows his subject regardless of methods is not supported by our observation. As a matter of fact, the results of such self-styled educators have been consistently poor. The knowing of a thing and imparting it to students are two very different entities. Such teachers usually shoot over the heads of their students, and do not know it. They contact the students as if they were their equals in age and experience. On the contrary, a number of teachers have come under my observation, whose knowledge of the subject was by no means perfect, but whose teaching results were excellent. They were educators by nature and training.

The major part of our interest in this study concerned with the retention power of the student. The prevalent method of examinations encourage desultory memory or "cramming," as it is commonly called, and leave association memory and reasoning power at a decided disadvantage. Every educator knows the shortcomings of such examinations, but very few have tried to remedy it. It is detrimental even to students with the so-called "photographic" memory. Association and reasoning is very essential in medicine, and this might be the reason why some of the "bright" students fail in medical practice. In my study and experience, I have found several means by which the retentive power of the student can be improved, but by far, the best results were attained by two methods: correlation, and balanced examinations.

Medical subjects in which correlation was neglected, suffered most severely. The retentive power of students dropped sharply after three months, and was exceedingly low after two years. The subject of embryology was the most abused course that came under my observation, histology was next, then neurology with gross anatomy faring better than any of the micro-

scopic subjects. Since embryology can be useful, if not more so than any of the anatomical studies, why is it neglected and why is it so poorly correlated with other medical studies? The answer to this is probably not far to seek. The value of embryology of medicine has remained to a large extent unknown in this country until quite recently. The discovery of the embryology of certain blood diseases has assisted in its resurrection. The neglect of embryology by the medical profession is undoubtedly a function of our teaching methods. The teachers of embryology might have been excellent embryologists; they might have taught the student the reading of the chick and pig embryo series; they might have pointed out the origin of this and that organ, but if they failed to impregnate the subject with the application of these and other data to medicine, embryology has lost its usefulness and value for medicine. The graduates of such courses, when they enter the practice of medicine, are neither able to utilize the resources of embryology to any extent, nor will they correlate embryology with their teaching when they become instructors in medicine. As to correlation, histology fares slightly better than embryology, but a great deal remains to be done before it means more to students and practitioners than a prerequisite course for pathology.

I have given balanced examinations to my students for the greater part of my teaching career. However, more serious attention has been paid to it the last ten years. Several observations focused my attention on the meaning of examination questions as a teaching tool, rather than a grading tool. Practically all students show a keen interest in "going over" previous examination questions, "to know how to study." A large number of students fail the course if they have not seen the previous examination questions, as in the case of a new instructor. My attention was particularly sharpened when nearly one-third of the class failed the course, because of change of methods in a neighboring institution.

In the preparation of balanced examinations, two major factors are considered; first, the teaching of the subject matter, and second, the training of the student's facilities. Both are considered of equal importance, and one can not exist without the other. The teaching of the subject matter includes the association of, and the application to medicine. The training aspect is concerned with factors that are essential in the making of a medical man and a scientist, i.e., power of observation, neatness, patience, accuracy, and perserverance. Considerable detail is expected in the early part of the course, which is mainly for the purpose of training. At the beginning of the course the training aspect is at a maximum; it gradually diminishes and is at a minimum at the end of the course. The subject matter is at a minimum at the start; it increases in volume as the course progresses, and is at a maximum at the end of the course. This may be illustrated graphically. Let us suppose that x stands for the subject matter and y for the training aspect. The exponents of x and y represent the approximate volume of each aspect. On basis of four examinations, it may be written as follows:

$$x + y^4 = z^5$$
$$x^2 + y^3 = z^5$$
$$x^3 + y^2 = z^5$$
$$x^4 + y = z^5$$

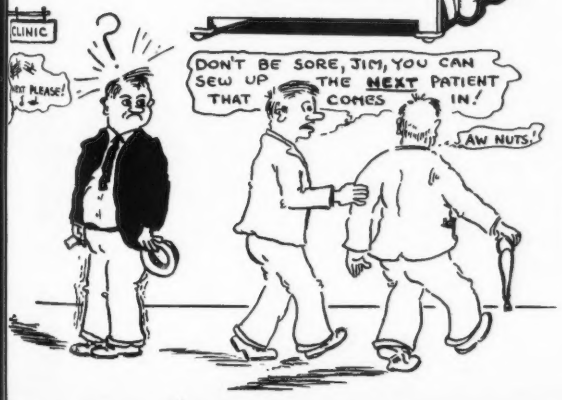
In my courses, I usually give four examinations during the course, two written and two practical. However, any number of examinations can be used. The value of the methods is the same even if only one examination is given during the course.

The objection may be raised that this method is concerned with balanced teaching rather than examinations. It is concerned with both, but the emphasis is placed on the examinations.

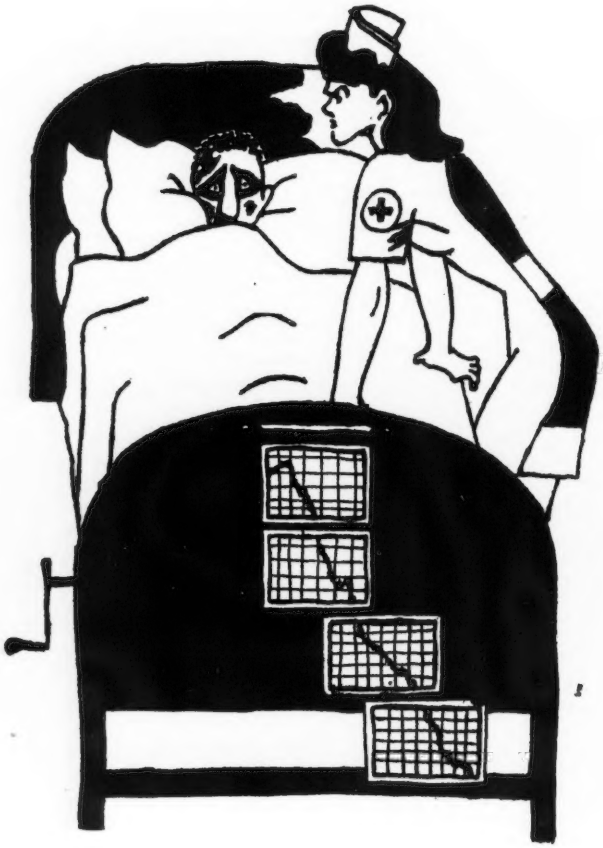
This method has given the most satisfactory results in any anatomical subject that I have been teaching. It keeps the student alert, and he soon learns that he studies anatomy for the sake of medicine, and not for the sake of passing examinations. The retentive power is increased, particularly if correlated in later studies. The time period is the same and the content is equivalent for all of the examinations. The final grade is the direct average of all the examinations given during the course.

THIS-N-THAT.

—AND THEY CAME WITHIN 3/5 OF BEING FAMOUS"



IS THAT ALL? SHUCKS! AND I HAD A HALF A BUCK BET WITH DIONNE!
YES, MR. DUVAL, YOU'RE THE PROUD FATHER OF TRIPLETS! TWO BOYS AND A GIRL.
KRIEGER '35



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—MEDICAL TID-BITS—

A doctor treated his patient for gonorrhea with penicillin. Five weeks later the patient displayed a primary sore of syphilis. The penicillin evidently lengthened the period of incubation of the spirochaete. The patient now claims that the injection given him by the doctor is the cause of syphilis, and he is trying to institute legal action against the physician.—"Leaves from a Doctor's Diary" by Maurice Chideckel. From the *Roche Review,* October 1947.

* * * *

"Degrees of Narcoticism."—John Snow, 1847.

In the first degree were included the various changes of feeling that a person may experience while he is still conscious of his surroundings and still able to direct his voluntary movements.

In the second degree mental functions may still be exercised, but in a distorted manner.

In the third degree there is no evidence of mental function and no voluntary motions.

In the fourth degree no movements are seen except those of respiration.

In the fifth degree (not witnessed in a human being), the respiratory movements are more or less paralyzed and become difficult, feeble, or irregular. —Thomas E. Keyes, *Journal of the History of Medicine,* October 1946.

* * * * *

"On April 12, 1829, Jules Cloquet, a French surgeon, had performed a (painless) mastectomy on a patient in mesmeric sleep."—*Mesmerism and Surgery,* George Rosen, *Journal of the History of Medicine, October* 1946.

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Contrary to common belief, heart disease is no more prevalent among medical men than it is among laymen.

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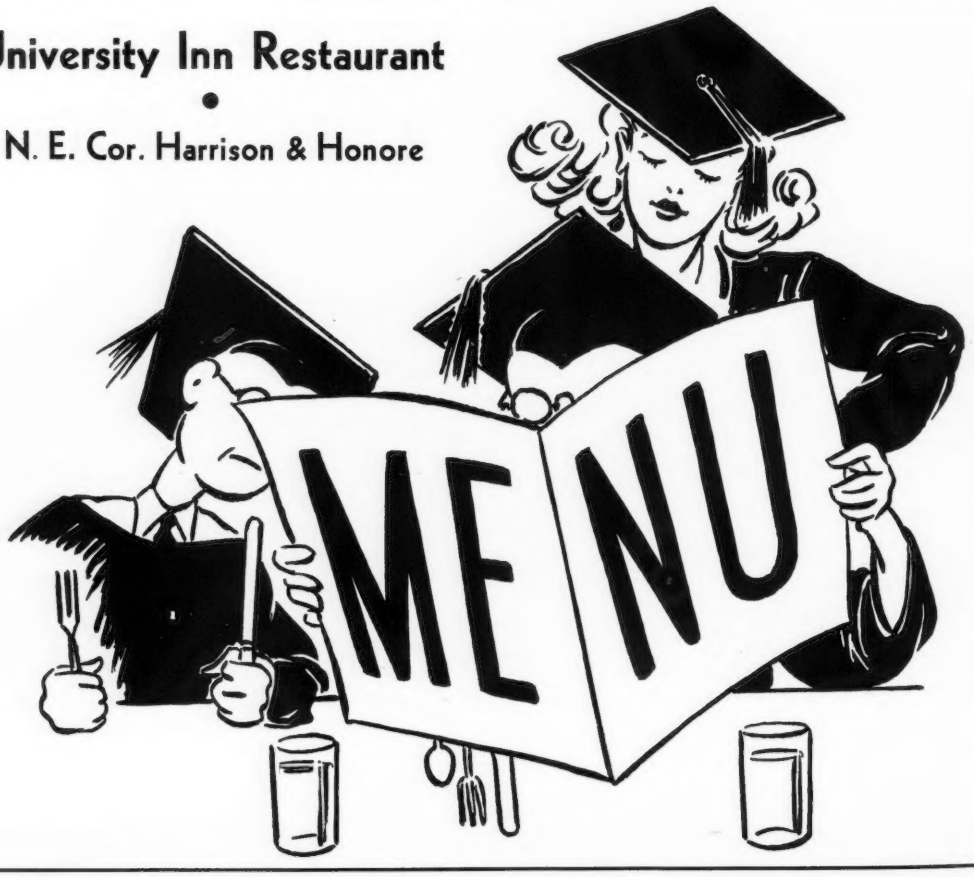

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— MEDICAL TID-BITS —

The Zunis of New Mexico have an ancient rite called the Urine Dance in which the participants drink freely of their urine.

The word opium is derived from the Greek word for juice, the drug being obtained from the juice of poppy capsules.

Between one-fourth and one-third of the adult population have blood pressures under 110 mm systolic and 70 mm diastolic.

Persons sixty-five years of age and over constituted 4.3 percent of the population of the United States in 1900, and 6.8 percent in 1940; the under-twenty group decreased from 44.3 percent to 34.5 percent.

"Was your friend shocked over the death of his mother-in-law?"

"Shocked? He was electrocuted!"—Clin. Med.

In Western Journal of Surgery, November '45, I read that a woman could be allergic to her husband's semen. This is one article I hope my wife doesn't hear about.—S.D.

Wharton of Wharton's duct, thought that the viscous fluid within the follicles of the thyroid gland lubricated the trachea. He also believed that the gland was larger in women to serve a cosmetic function in giving grace to the contour of the neck.

A tuberculous woman may bear the first confinement well; the second, with difficulty; the third, never.—Dubois.

Man has lived where the temperature falls as low as —157° F.

Medicine: The art of coming to a conclusion on insufficent evidence.

* * * * *

"The first wealth is health. Sickness is poor-spirited, and cannot serve anyone; it must husband its resources to live. But health answers its own ends, and has to spare; runs over, and inundates the neighborhoods and crooks of other men's necessities."

—Ralph Waldo Emerson

—The Doctor

One pound of learning requires 10 pounds of common sense to apply it.—Persian Proverb.

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